1. NAME OF THE MEDICINAL PRODUCT

Casirivimab and Imdevimab 120 mg/mL solution for injection or infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Co-packaged 6 mL single-use vials

Each casirivimab 6 mL vial contains 300 mg of casirivimab per 2.5 mL (120 mg/mL).

Each imdevimab 6 mL vial contains 300 mg imdevimab per 2.5 mL (120 mg/mL).

Co-packaged 20 mL multidose vials

Each casirivimab 20 mL multidose vial contains 1 332 mg of casirivimab per 11.1 mL (120 mg/mL).

Each imdevimab 20 mL multidose vial contains 1 332 mg imdevimab per 11.1 mL (120 mg/mL).

Casirivimab and Imdevimab are two neutralising 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 (sterile concentrate).
Clear to slightly opalescent and colourless to pale yellow solution with a pH of 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Casirivimab and Imdevimab is indicated for the treatment of confirmed COVID-19 in patients aged 12 years and older and weighing at least 40 kg that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19.

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

4.2 Posology and method of administration

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Preparation and administration of Casirivimab and Imdevimab should be initiated and monitored by a qualified healthcare provider using 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.

Posology

Treatment
The dosage in patients 12 years of age and older weighing at least 40 kg 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).

Casirivimab with Imdevimab should be given together as soon as possible after a positive viral test for SARS-CoV-2.

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).

Special Populations

Renal Impairment
No dosage adjustment is required in individuals with mild or moderate renal impairment, or in 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).

Pediatric 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 pediatric individuals ≥ 12 years of age and older and weighing ≥ 40 kg (see section 5.2).

Method of administration

Casirivimab and Imdevimab is for intravenous infusion.

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

Table 1: Recommended Dilution Instructions for Casirivimab and Imdevimab for IV Infusion

Indication	**Casirivimab and Imdevimab Dose (Total)**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial and inject into a prefilled 0.9% sodium chloride or 5% dextrose infusion bag**
Treatment	600 mg casirivimab and 600 mg imdevimab (1200 mg dose)	10 mL	2.5 mL from two 6 mL single -use vials of casirivimab 2.5 mL from two 6 mL single-use vial of imdevimab
			5.0 mL from one 20 mL multidose vial of casirivimab 5.0 mL from one 20 mL multidose vial of imdevimab
			2.5 mL from two 6 mL single-use vials of casirivimab 5.0 mL from one 20 mL multidose vial of imdevimab
			5.0 mL from one 20 mL multidose vial of casirivimab 2.5 mL from two 6 mL single-use vials of imdevimab

Table 2: Minimum Infusion Time for IV Infusion Bag Volumes for diluted 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 600 mg casirivimab and 600 mg imdevimab (1 200 mg)	Minimum Infusion Time 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.

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.

Hypersensitivity Reactions including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of Casirivimab and Imdevimab. 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 and 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.

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 metabolized 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 impact 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 COVID-19 vaccine was permitted and no safety concerns identified.

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 are insufficient with respect to reproductive toxicity. In a tissue cross-reactivity study with casirivimab and imdevimab using human fetal 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 fetus. Casirivimab and Imdevimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus 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 fetus is unknown.

Breast-feeding

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 breast-feeding for the child and the benefit of therapy for the woman. Breast-feeding 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 ability to drive and use machines

Casirivimab and Imdevimab has 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 Casirivimab and Imdevimab in clinical trials which support the listed indications. 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). Expanded analysis has also been performed on safety data from the supportive studies (COV-20145, HV-2093).

Reported adverse drug reactions (ADRs) identified from the clinical development program 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 3 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 3: 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

[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)

Description of selected adverse reactions

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

Anaphylaxis/anaphylactic reaction has been observed in the clinical development program 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 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).

Pediatric Population

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

Elderly

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 reporting system at www.fda.gov.ph and to the Roche (Philippines) Inc. Local Safety Unit via email at philippines.drug_safety@roche.com.

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

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

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

Mechanism of action

Casirivimab (IgG1κ) and Imdevimab (IgG1λ) are two recombinant human monoclonal antibodies which are unmodified in the Fc regions. Casirivimab and Imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants K_D = 45.8 pM and 46.7 pM, respectively. Casirivimab, imdevimab and casirivimab and 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.

Antiviral activity

In a SARS-CoV-2 virus neutralization assay in Vero E6 cells, casirivimab, imdevimab, and casirivimab and imdevimab together neutralized 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.

Antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) were assessed using Jurkat target cells expressing SARS-CoV-2 spike protein. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCC with human natural killer (NK) effector cells. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCP with human macrophages. Casirivimab, imdevimab and casirivimab and imdevimab together did not mediate complement-dependent cytotoxicity in cell-based assays.

Antibody Dependent Enhancement (ADE) of Infection

The potential of casirivimab and of imdevimab to mediate viral entry was assessed in immune cell lines co incubated with recombinant vesicular stomatitis virus (VSV) pseudoparticles expressing SARS-CoV-2 spike protein at concentrations of monoclonal antibodies down to approximately 10 fold below the respective neutralization EC50 values. Casirivimab and imdevimab together and imdevimab alone, but not casirivimab alone, mediated entry of pseudoparticles into FcγR2+ Raji and FcγR1+/FcγR2+ THP1 cells (maximum infection in total cells of 1.34% and 0.24%, respectively, for imdevimab; 0.69% and

0.06%, respectively for casirivimab and imdevimab together), but not any other cell lines tested (IM9, K562, Ramos and U937 cells).

Antiviral 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. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

A key element in the development of casirivimab and imdevimab is to have 2 antibodies that bind to distinct, non-overlapping epitopes of the SARS-CoV-2 S protein to reduce the likelihood of viral resistance. The neutralization potency of casirivimab alone, imdevimab alone, 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).

See Table 5 for a comprehensive list of pseudotyped virus-like particles (VLP) encoding full sequences or key S protein substitutions of Variants of Concern/Interest assessed for susceptibility to casirivimab and imdevimab alone and together. Casirivimab and imdevimab retain neutralization potency against all the Variants of Concern/Interest shown in Table 4 even if one of the antibodies is impacted. Therefore, Casirivimab and Imdevimab is expected to retain activity against these Variants of Concern/Interest.

Table 4: Pseudotyped Virus-Like Particle Neutralization 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[d]	no change[d]	no change[d]
B.1.351 (South Africa origin/Beta)	Full S protein[b]	no change[d]	45-fold	no change[d]
P.1 (Brazil origin/Gamma)	Full S protein[c]	no change[d]	418-fold	no change[d]
B.1.427/B.1.429 (California origin/Epsilon)	L452R	no change[d]	no change[d]	no change[d]
B.1.526 (New York origin/Iota)[e]	E484K	no change[d]	25-fold	no change[d]
B.1.617.1/B.1.617.3 (India origin/Kappa)	L452R+E484Q	no change[d]	7-fold	no change[d]
B.1.617.2 (India origin/Delta)	L452R+T478K	no change[d]	no change[d]	no change[d]

[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] No change: ≤ 5-fold reduction in susceptibility.
[e] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).
*Variants of interest/concern as defined by the Centers for Disease Control and Prevention (CDC, 2021) {https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html}

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

Table 5: Neutralization Data for Authentic SARS-CoV-2 Variants 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]
B.1.617.1 (India origin/Kappa)	no change[a]	6-fold	no change[a]

[a] No change: ≤ 5-fold reduction in susceptibility.

See Table 6 for a comprehensive list of variants with a ≥ 5-fold reduced susceptibility to casirivimab alone, or imdevimab alone, or casirivimab and imdevimab together.

Table 6: **Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variants that Impact Neutralization Potency of casirivimab and imdevimab Alone or Together**

SARS-CoV-2 Variant	Reduced Susceptibility to casirivimab and imdevimab together	Reduced Susceptibility to casirivimab	Reduced Susceptibility to imdevimab
K417E	no change[a]	182-fold	no change[a]
K417N	no change[a]	7-fold	no change[a]
K417R	no change[a]	61-fold	no change[a]
Y453F	no change[a]	> 438-fold	no change[a]
L455F	no change[a]	80-fold	no change[a]
E484K	no change[a]	25-fold	no change[a]
F486V	no change[a]	> 438-fold	no change[a]
Q493K	no change[a]	> 438-fold	no change[a]
K444N	no change[a]	no change[a]	> 755-fold
K444Q	no change[a]	no change[a]	> 548-fold
K444T	6-fold	no change[a]	> 1033-fold
V445A	no change[a]	no change[a]	548-fold
V445T	no change[a]	107-fold	no change[a]
E406D	no change[a]	51-fold	no change[a]
G485D	no change[a]	5-fold	no change[a]
G476S	no change[a]	5-fold	no change[a]
F486L	no change[a]	61-fold	no change[a]
F486S	no change[a]	> 715-fold	no change[a]
P337L	no change[a]	no change[a]	5-fold
N439K	no change[a]	no change[a]	463-fold
N440K	no change[a]	no change[a]	28-fold
K444L	no change[a]	no change[a]	153-fold
K444M	no change[a]	no change[a]	1577-fold
G446V	no change[a]	no change[a]	135-fold
N450D	no change[a]	no change[a]	9-fold
Q498H	no change[a]	no change[a]	17-fold
P499S	no change[a]	no change[a]	206-fold
E484Q	no change[a]	19-fold	no change[a]
Q493E	no change[a]	446-fold	no change[a]
G476D	no change[a]	1021 fold	no change[a]

[a] No change: < 5-fold reduction in susceptibility.

See Table 7 for a comprehensive list of variants with a < 5-fold reduced susceptibility to casirivimab alone, imdevimab alone, and casirivimab and imdevimab together.

Table 7: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with casirivimab and imdevimab together. SARS-CoV-2 Variants That Do Not Impact Neutralization Potency of either casirivimab nor imdevimab Alone or Together.

SARS-CoV-2 S Protein Variant					
L18F	R346E	V382L	K458N	G485D	H519Q
W152C	R346G	P384L	K458R[a]	G485S	A520S
A222V	R346K	P384S	I468V	F490L	A522S
Q321L[a]	A348T[a]	R403K	T470I	F490P	A522V
P322A	A352S	R408I[a]	E471Q	F490S	K537R
T323I	N354D[a]	Q409E[a]	I472V[a]	F490Y	D614G
P330S	N354S	Q414E	A475V	S494P	D614N
E340A	S359N[a]	Q414R	S477N	N501Y	V687G
E340D	V367F[a]	A435S[a]	T478I	G504D	V1128A
E340K	N370S	N439V	T478K	G504S	
V341I[a]	A372T	L441Q	P479S	Y508H[a]	
A344S[a]	F377L	Y449N	V483A[a]	E516Q	
T345P	K378R[a]	L452R	V483F	H519P[a]	

[a] Not assessed for casirivimab and imdevimab together

It is not known how *in vitro* neutralization data correlate with clinical outcomes.

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.

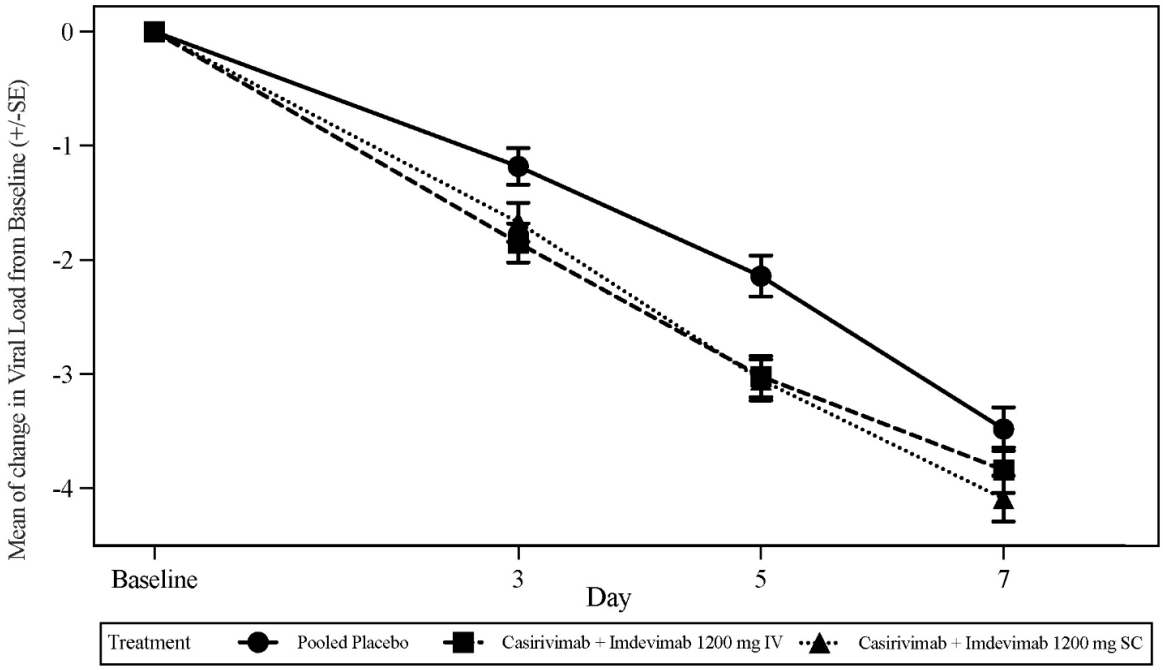
Pharmacodynamic effects

Trial COV-2067 evaluated Casirivimab and Imdevimab 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 Casirivimab and Imdevimab 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.

COV-20145
COV-20145 is a Phase 2 randomized, double-blind, placebo-controlled, parallel group study to assess the dose response profile of single IV or single subcutaneous doses of Casirivimab and Imdevimab 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 patients not at high risk of severe disease (symptomatic with no risk factors / asymptomatic). Subjects were randomized into treatment arms and placebo arms including 116 subjects who were randomized to receive an IV dose of 1 200 mg of Casirivimab and Imdevimab (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 Casirivimab and Imdevimab resulted in a statistical 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 randomized, double-blinded, placebo-controlled clinical trial evaluating Casirivimab and Imdevimab for the treatment of subjects with COVID-19 who are not hospitalized.

In the COV-2067 Phase 3 trial, 4 567 subjects with at least one risk factor for severe COVID-19 were randomized to a single intravenous infusion of Casirivimab and Imdevimab 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) (n = 838), Casirivimab and Imdevimab 2 400 mg (1 200 mg of casirivimab and 1 200 mg of imdevimab) (n = 1 529), Casirivimab and Imdevimab 8 000 mg (4 000 mg of casirivimab and 4 000 mg of imdevimab) (n = 700), or placebo (n = 1 500) groups. The two Casirivimab and Imdevimab 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 randomized to the specific Casirivimab and Imdevimab dose and subjects who were concurrently randomized to placebo.

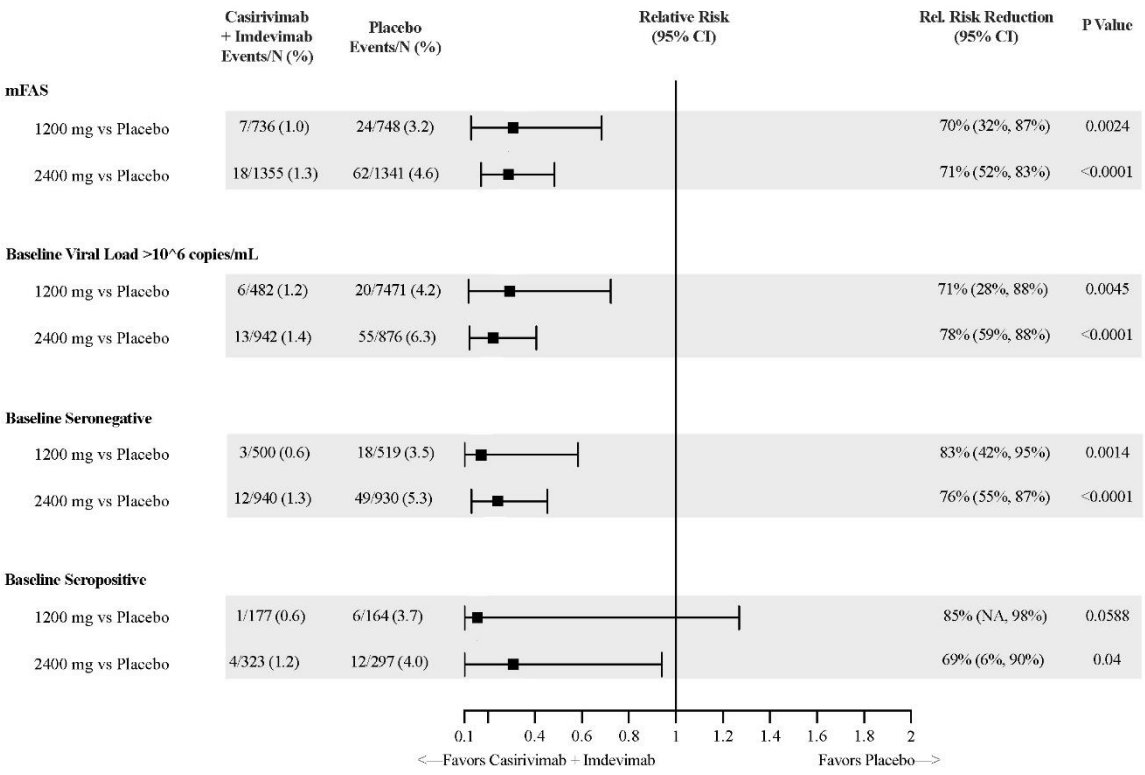
At baseline, in all randomized subjects with at least one risk factor, the median age was 50 years (with 13% of subjects ages 65 years or older), 52% of the subjects were female, 84% were White, 5% were Black or African American; 36% identified as Hispanic or Latino. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

Primary endpoint

The primary endpoint was the proportion of subjects with ≥ 1 COVID-19-related hospitalization or all-cause death through Day 29, in subjects with a positive SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab at randomization, and with at least one risk factor for severe COVID-19, i.e., the modified full analysis set (mFAS). In the mFAS, events (COVID-19-related hospitalization or all-cause death through Day 29) occurred in 7 (1.0%) subjects treated with Casirivimab and Imdevimab 1 200 mg compared to 24 (3%) subjects concurrently randomized to placebo, demonstrating a 70% reduction in COVID-19-related hospitalization or all-cause death compared to placebo (p = 0.0024). Events occurred in 18 (1.3%) subjects treated with Casirivimab and Imdevimab 2 400 mg compared to 62 (5%) subjects concurrently randomized to placebo, demonstrating a 71% reduction compared to placebo Casirivimab and Imdevimab 1% vs placebo 5%, p < 0.0001).

In the 1 200 mg analysis, there was 1 death each in the Casirivimab and Imdevimab and placebo arm (p = 1.0); and in 2 400 mg analysis, there were 1 and 3 deaths, respectively, in the Casirivimab and Imdevimab and placebo arms (p = 0.3721). Overall, similar effects were observed for Casirivimab and Imdevimab 1200 mg (600 mg of casirivimab and 600 mg of imdevimab) and Casirivimab and Imdevimab 2 400 mg (1200 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 or serologic status.

Figure 2: COVID-19-Related Hospitalizations or All-Cause Death through Day 29 in Study COV-2067



Key Secondary Endpoints

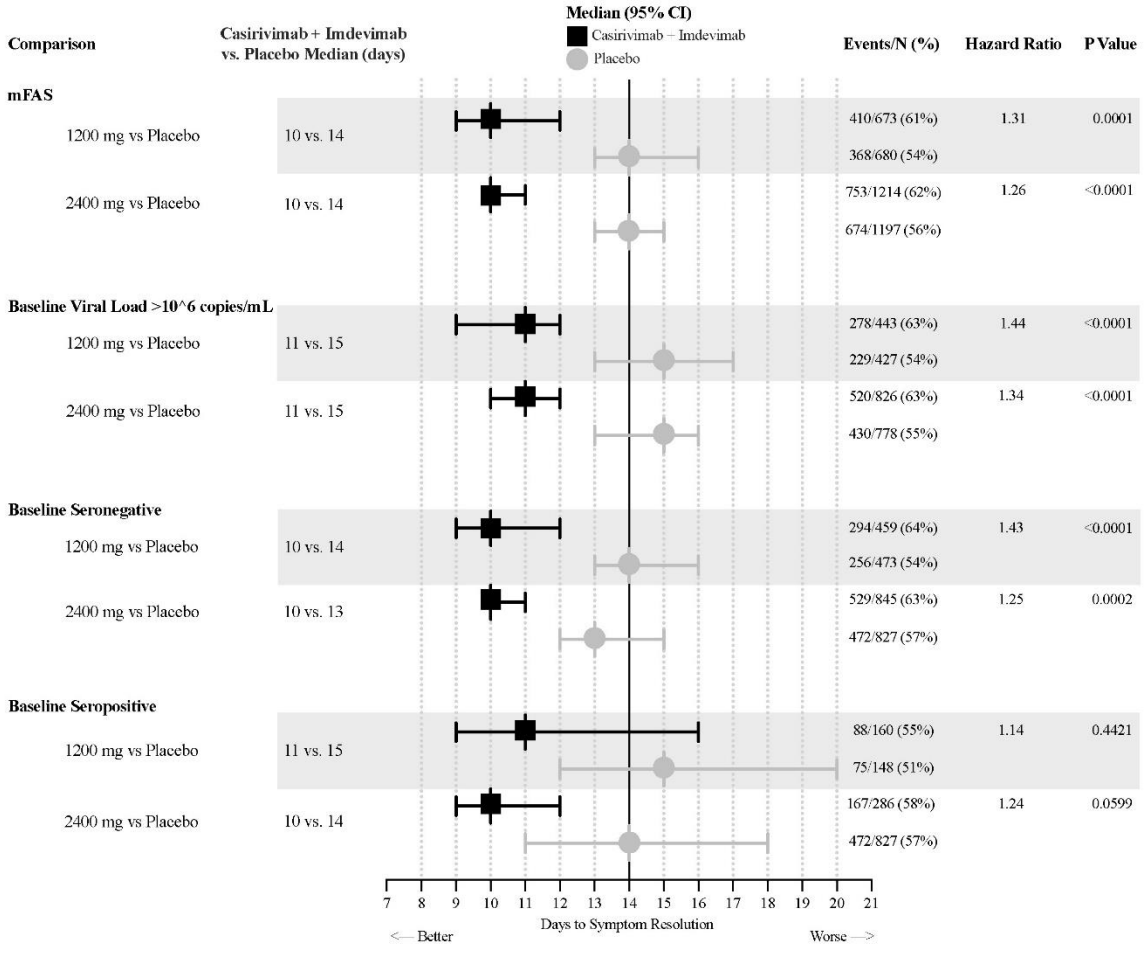
Time to COVID-19 symptom resolution

The median time to symptom resolution, as recorded in a trial-specific daily symptom diary, was 10 days for Casirivimab and Imdevimab treated subjects, as compared with 14 days for placebo-treated subjects (p = 0.0001) (see Table 8) for 1 200 mg vs. placebo; p < 0.0001 for 2 400 mg vs. placebo). Treatment with Casirivimab and Imdevimab resulted in a 4 days shorter median time to COVID-19 symptom resolution compared to placebo-treated subjects (see Figure 3).

Table 8: Summary of Key Phase 3 Results from Study COV-2067

	1 200 mg IV	Placebo	2 400 mg IV	Placebo
	n = 736	n = 748	n = 1 355	n = 1 341
Patients with ≥1 COVID-19-related hospitalization or death through day 29				
Risk reduction	70% (p = 0.0024)		71% (p < 0.0001)	
# of patients with events	7 (1.0%)	24 (3.2%)	18 (1.3%)	62 (4.6%)
Time to COVID-19 symptom resolution				
Median days to symptom resolution	10	14	10	14
Median reduction (days)	4 (p < 0.0001)		4 (p < 0.0001)	

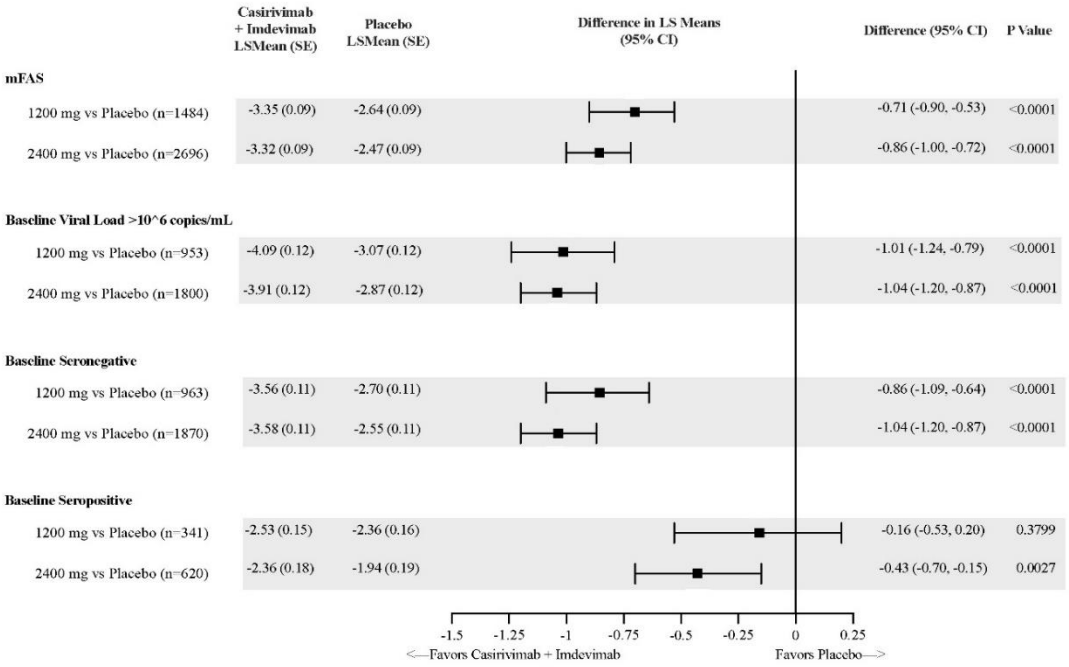
Figure 3: Time to Symptom Resolution in Study COV-2067



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 Casirivimab and Imdevimab resulted in a statistically significant 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 Casirivimab and Imdevimab 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; $p < 0.0001$). Figure 4 shows the mean change from baseline in SARS-COV-2 viral load at Day 7.

Figure 4: Change from Baseline in SARS-COV-2 Viral Load (log_{10} copies/mL) at Day 7 with Treatment with 1200 mg (600 mg casirivimab and 600 mg imdevimab) vs Placebo or 2400 mg (1 200 mg casirivimab and 1 200 mg imdevimab) vs Placebo in Study COV-2067



For the primary and key secondary endpoints, results were consistent across subgroups of patients defined by nasopharyngeal viral load > 10^6 copies/mL at baseline or serologic status.

5.2 Pharmacokinetic properties

Both casirivimab and imdevimab exhibited linear and dose-proportional pharmacokinetics (PK) between 300 mg Casirivimab and Imdevimab (150 mg casirivimab and 150 mg imdevimab) to 8 000 mg Casirivimab and Imdevimab (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 9.

Table 9: Summary of PK Parameters (for casirivimab and imdevimab) After a Single 1 200 mg IV Dose of Casirivimab and Imdevimab

PK Parameter[1]	casirivimab	imdevimab
AUC_{0-28} (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 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

Absorption

Based on population pharmacokinetic modeling, mean (standard deviation) C_{max} and C_{28} estimates for casirivimab and imdevimab following single IV dose 1 200 mg (600 mg each monoclonal antibody) are listed in Table 9.

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 10.

Table 10: 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)	0.188	(0.11, 0.3)	0.227	(0.15, 0.35)

Excretion

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

Pediatric 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.

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 has 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.

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 fetal tissues, no binding was detected.

For the single-dose treatment, 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 Casirivimab and Imdevimab 1200 mg (600 mg of casirivimab and 600 mg of imdevimab) IV.

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

Unopened vial: 3 months

Co-packaged 20 mL 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 refrigerated between 2 °C to 8 °C. Beyond these times and conditions, in-use storage is the responsibility of the user.

Co-packaged 6 mL single-use vials

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

Diluted Solution for IV 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 IV infusion bag to equilibrate to room temperature for approximately 30 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

Casirivimab and Imdevimab is provided in clear Type 1 glass vials in 20 mL or 6 mL vials.
Each carton contains 2 vials per package:

Casirivimab and Imdevimab 120 mg/mL solution for infusion or injection, multidose vials

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.

Casirivimab and Imdevimab 120 mg/ml solution for infusion or injection, single-use vial

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

General precautions

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

Preparation of Casirivimab and Imdevimab for Intravenous Infusion

Casirivimab and Imdevimab 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 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, colorless 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 infusion bag by inversion. Do not shake.
6. Casirivimab and Imdevimab 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.

Administration of Casirivimab and Imdevimab 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 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.

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. EMERGENCY USE AUTHORISATION (EUA) HOLDER

Roche (Philippines) Inc.

8. AUTHORISATION NUMBER(S)

N/A

9. DATE OF FIRST AUTHORISATION

Emergency Use Authorization granted on 01 October 2021

10. DATE OF REVISION OF THE TEXT

August 2021
Reference: EU SmPC

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, please report to the Food and Drug Administration (FDA) at www.fda.gov.ph and to the Roche (Philippines) Inc. Local Safety Unit via email at philippines.drug_safety@roche.com

At the first sign of any adverse drug reaction, the patient should seek medical attention immediately.

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