This is a Recommendation for Use from Roche Pharma (Schweiz) AG for Healthcare Professionals for Casirivimab/Imdevimab, concentrate for solution for infusion, which has not undergone Swissmedic's assessment yet and therefore has not been authorized by Swissmedic. On the basis of Art. 21 para. 1 of Ordinance 3 on Measures to Combat the Coronavirus (COVID-19) the medicinal products to treat COVID-19 can be placed on the market immediately after submission to Swissmedic. This applies during Swissmedic's assessment and until a decision on a marketing authorization has been made.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

Recommendation for Use from Roche Pharma (Schweiz) AG (not authorized by Swissmedic)

Updated by Roche Pharma (Schweiz) AG on 19.04.2021

1. NAME OF THE MEDICINAL PRODUCT

Casirivimab and Imdevimab 120 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each casirivimab 20 mL vial contains 1332 mg of casirivimab per 11.1 mL (120 mg/mL) and each imdevimab 20 mL vial contains 1332 mg imdevimab per 11.1 mL (120 mg/mL).

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

Casirivimab and imdevimab are human immunoglobulin G-1 (IgG1) 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

Concentrate for solution for infusion.

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

Risk factors may include but are not limited to:

- Advanced age
- Obesity
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Type 1 or type 2 diabetes mellitus
- Chronic kidney disease, including those on dialysis
- Chronic liver disease
- Immunosuppressed, based on prescribers's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, and prolonged use of immune-weakening medications.

Limitation in Patients with Severe COVID-19
Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

4.2. Posology and method of administration

Treatment with casirivimab and imdevimab must be initiated and monitored by a qualified healthcare provider. Treatment should be given under conditions where management of an infusion reaction/allergic reaction is possible.

Casirivimab and imdevimab must be administered together as a single intravenous infusion.

Posology
The recommended dose of casirivimab and imdevimab is

- 1200 mg of casirivimab and 1200 mg of imdevimab administered as a single intravenous infusion (see Table 9)

Special Populations
Renal Impairment
No dosage adjustment is required in patients with renal impairment (see section 5.2).

Hepatic Impairment
The pharmacokinetics of casirivimab and imdevimab have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of casirivimab and imdevimab in children under 12 years of age have not yet been established. No data are available. No dosage adjustment is recommended in paediatric patients who are 12 years of age and older (see section 5.2).

Method of administration
Casirivimab and imdevimab are for administration by intravenous infusion. Do not administer as an intramuscular (IM) injection or subcutaneous (SC) injection.

For instructions on the dilution of casirivimab and imdevimab, see section 6.6.

Administer casirivimab and imdevimab as an intravenous infusion through an intravenous line containing a sterile, in-line or add-on 0.2-micron filter.

The rate of infusion may be slowed or interrupted if the patient develops any signs of infusion-associated events or other adverse events. Patients should be monitored during the infusion and for at least one hour after the completion of the infusion (see section 4.4).

4.3. Contraindications

Hypersensitivity to casirivimab or imdevimab 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 including Infusion-Related Reactions
Serious 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 have been observed with administration of casirivimab and imdevimab. These reactions may be severe or life threatening. Signs and symptoms of infusion related reactions may include, but are not limited to, fever, difficulty breathing, reduced oxygen saturation, chills, nausea, arrhythmia (e.g. atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness, fatigue, and diaphoresis. If an infusion-related reaction occurs, consider 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.

Immune Response
An interaction with COVID-19 vaccinations has not been studied and therefore cannot be excluded.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are limited amount of data from the use of casirivimab and imdevimab in pregnant women. Animal reproductive toxicity studies have not been conducted, however, in a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, no binding of clinical concern was detected (see section 5.3). Human immunoglobulin G1 (IgG1) antibodies are known to cross the

placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. 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.

Breast-feeding
There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for casirivimab and imdevimab and any potential adverse effects on the breastfed child from casirivimab and imdevimab or from the underlying maternal condition. Breastfeeding individuals 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 have no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

Overall, more than 13,000 subjects have been exposed to intravenous casirivimab and imdevimab in clinical trials including healthy volunteers and patients.

The safety profile of casirivimab and imdevimab are based on analyses of data from R10933-10987-COV-2067, a randomized, double-blind, placebo-controlled Phase 1/2 (n=799) and Phase 3 (n=5,531) trial in ambulatory (non-hospitalised) adults with mild to moderate COVID-19 symptoms who had a sample collected for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion

Phase 3 Data
Subjects were treated with a single infusion of 1,200 mg (600 mg casirivimab and 600 mg imdevimab) (n=827), or 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) (n=1,849), or 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) (n=1,012), or placebo (n=1,843). Only the following adverse events were collected during the study: the adverse events collected were infusion related reactions and hypersensitivity reactions of moderate severity or higher, all serious adverse events (SAEs), and any treatment-related adverse event that led to a medically attended visit up to day 29.

Serious adverse events were reported in 9 subjects (1.1%) in the casirivimab and imdevimab 1,200 mg group, 24 subjects (1.3%) in the casirivimab and imdevimab 2,400 mg group, 17 subjects (1.7%) in the casirivimab and imdevimab 8,000 mg group, and 74 subjects (4.0%) in the placebo group. The majority of SAEs were related to COVID-19 and its complications. A total of 5 patients (0.3%) experienced fatal events in the placebo group and 1 patient (0.1%) in each casirivimab and imdevimab group. None of the fatal events were considered to be related to study treatment. Casirivimab and imdevimab are not recommended at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).

Phase 1/2 Data
Additional safety data from the Phase 1/2 portion of the trial included subjects who were treated with a single infusion of 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) (n=258) or 8,000 mg

(4,000 mg casirivimab and 4,000 mg imdevimab) (n=260), or placebo (n=262). Only the following adverse events were collected during the study: infusion-related reactions and hypersensitivity reactions of moderate severity or higher through day 29, all serious adverse events (SAEs); and in phase 1 only, all grade 3 and 4 treatment-emergent adverse events.

Serious adverse events were reported in 4 subjects (1.6%) in the casirivimab and imdevimab 2,400 mg group, 2 subjects (0.8%) in the casirivimab and imdevimab 8,000 mg group, and 6 subjects (2.3%) in the placebo group. None of the SAEs were considered to be related to study drug. SAEs that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia, nausea and vomiting (2,400 mg casirivimab and imdevimab), intestinal obstruction and dyspnea (8,000 mg casirivimab and imdevimab) and COVID-19, pneumonia and hypoxia (placebo). Casirivimab and imdevimab are not recommended at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).

Tabulated summary of adverse reactions

Table 1 shows the adverse reactions ranked under headings of system organ class and frequency using the following convention: 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); Not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions:

System organ class	Frequency	Adverse Reaction
Injury, poisoning and procedural complications	Uncommon	Infusion related reactions[1]

[1] Symptoms reported as IRRs are described below in 'Hypersensitivity including anaphylaxis and Infusion-related reactions'. IRRs were pooled between the 1,200 mg, 2,400 mg and 8,000 mg doses.

Description of selected adverse reactions

Hypersensitivity Including Anaphylaxis and Infusion-related Reactions

One anaphylactic reaction was reported in the clinical program. The event began within 1 hour of completion of the infusion, and required treatment including epinephrine. The event resolved.

In the Phase 3 portion of the trial, infusion-related reactions of grade 2 or higher severity, were reported in 2 subjects (0.2%) in the 1,200 mg (600 mg casirivimab and 600 mg imdevimab) arm, 1 subject (0.1%) in the 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm, and 3 subjects (0.4%) in the 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and include nausea, dizziness, headache, hyperhidrosis, hyporesponsive to stimuli, rash, and vomiting. One hypersensitivity reaction (urticaria) was reported in the placebo arm.

In the Phase 1/2 portion of the trial, infusion-related reactions, of grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and included pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm and none were reported in the 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm.

Overall, in Phases 1/2 and 3, three subjects receiving the 8,000 mg dose of casirivimab and imdevimab, and in one subject receiving the 2,400 mg dose of casirivimab and imdevimab, the infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. All events resolved (see section 4.4).

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 to Roche via their website www.roche.com/products/local_safety_reporting.htm .

4.9. Overdose

There is no human experience of acute overdosage with casirivimab and imdevimab. Doses up to 8,000 mg (4,000 mg each of casirivimab and imdevimab, greater than 3 times the lowest recommended dose) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with casirivimab and imdevimab.

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 and imdevimab are a combination of two recombinant human IgG1 mAbs which are unmodified in the Fc regions, where each antibody targets the spike protein of SARS-CoV-2. Casirivimab and imdevimab exhibits neutralization activity with a concentration of 31.0pM (0.005 µg/mL) providing inhibition of 50% of viral infection in a plaque-reduction assay (PRNT50). Casirivimab and imdevimab binds to non-overlapping epitopes of the spike protein receptor binding domain (RBD). The blockage of the spike protein interaction with angiotensin-converting enzyme 2 (ACE2) leads to inhibition of infection of host cells.

Antiviral activity
In a SARS-CoV-2 virus neutralization assay in Vero E6 cells, casirivimab, imdevimab, and casirivimab and imdevimab neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with a concentration of 37.4pM (0.006 µg/mL), 42.1pM (0.006 µg/mL), and 31.0pM (0.005 µg/mL) respectively, providing inhibition of 50% of viral infection in a plaque-reduction assay (PRNT50).

The in vivo effect of casirivimab and imdevimab have been assessed in rhesus macaques and Syrian golden hamsters. Therapeutic administration of casirivimab and imdevimab at 25 mg/kg or 150 mg/kg in rhesus macaques infected with SARS CoV-2 resulted in accelerated viral clearance in nasopharyngeal swabs and oral swabs, as well as reduced lung pathology, relative to placebo-treated animals. Therapeutic administration of casirivimab and imdevimab at 5 mg/kg and 50 mg/kg doses in SARS-CoV-2 infected hamsters provided a therapeutic benefit as demonstrated by limited weight loss relative to placebo treated animals.

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.

Escape variants were identified following two passages in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following two passages in the presence of casirivimab and imdevimab together. Variants which showed reduced susceptibility to casirivimab alone included those with spike protein amino acid substitutions K417E (182-fold), K417N (7-fold), K417R (61-fold), Y453F (>438-fold), L455F (80-fold), E484K (25-fold), F486V (>438-fold) and Q493K (>438-fold). Variants which showed reduced susceptibility to imdevimab alone included substitutions K444N (>755-fold), K444Q (>548-fold), K444T (>1,033-fold), and V445A (548-fold). Casirivimab and imdevimab together showed reduced susceptibility to variants with K444T (6-fold) and V445A (5-fold) substitutions.

In neutralization assays using VSV pseudotyped with 39 different spike protein variants identified in circulating SARS-Cov-2, variants with reduced susceptibility to casirivimab alone included those with Q409E (4-fold), G476S (5-fold) and S494P (5-fold) substitutions, and variants with reduced susceptibility to imdevimab alone included one with the N439K (463-fold) substitution. Additional substitutions that were tested in pseudovirus assays and had reduced activity to casirivimab alone included E484Q (9-fold) and Q493E (446-fold). Casirivimab and imdevimab together retained activity against all variants tested.

Casirivimab and imdevimab individually and together retained neutralization activity against pseudovirus expressing all spike protein substitutions found in the B.1.1.7 lineage (UK origin) and against pseudovirus expressing only N501Y found in B.1.1.7 and other circulating lineages (Table 2). Casirivimab and imdevimab together retained neutralization activity against pseudovirus expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.1351 lineage (South Africa origin), and against K417T+E484K, found in the P.1 lineage (Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudovirus expressing K417N or E484K, as indicated above. The E484K substitution is also found in the B.1.526 lineage (New York origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (California origin).

Table 2: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

Lineage with Spike Protein Substitution	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y[a]	no change[c]
B.1.351 (South Africa origin)	K417N, E484K, N501Y[b]	no change[c]
P.1 (Brazil origin)	K417T + E484K	no change[c]
B.1.427/B.1.429 (California origin)	L452R	no change[c]
B.1.526 (New York origin)[d]	E484K	no change[c]

[a] Pseudovirus 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] Pseudovirus 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] No change: <2-fold reduction in susceptibility.
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

It is not known how pseudovirus data correlate with clinical outcomes.

In clinical trial R10933-10987-COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction ≥15%, which was detected in 3/66 subjects who had nucleotide sequencing data, each at a single time point (two at baseline in subjects from placebo and 2,400 mg casirivimab and imdevimab groups, and one at Day 25 in a subject from the 8,000 mg casirivimab and imdevimab group). The G446V variant had reduced susceptibility to imdevimab of 135-fold compared to wild-type in a VSV pseudoparticle neutralization assay but retained susceptibility to casirivimab alone and casirivimab and imdevimab together.

It is possible that resistance-associated variants to casirivimab and imdevimab together could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

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

Pharmacodynamic effects

Trial R10933-10987-COV-2067 evaluated casirivimab and imdevimab with doses of up to 6.66 times the lowest recommended dose (600 mg casirivimab and 600 mg imdevimab; 1,200 mg casirivimab and 1,200 mg 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.

Clinical efficacy and safety

The data are based on analyses of data from the Phase 1/2/3 R10933-10987-COV-2067 adaptive trial. R10933 10987 COV 2067 is a randomized, double blinded, placebo controlled clinical trial studying casirivimab with imdevimab for the treatment of adult subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). The trial enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 viral infection determination.

Phase 3 Data from R10933-10987-COV-2067

In the Phase 3 portion of the trial, 4,567 subjects were randomized to receive a single intravenous (IV) infusion of 1,200 mg dose (600 mg of casirivimab and 600 mg of imdevimab) (n=838), or 2,400 mg dose (1,200 mg of casirivimab and 1,200 mg of imdevimab) (n=1,529), or 8,000 mg dose (4,000 mg of casirivimab and 4,000 mg of imdevimab) (n=700), or placebo (n=1,500). The two casirivimab with imdevimab doses at the start of Phase 3 were 8,000 mg and 2,400 mg; based on Phase 1/2 efficacy analyses showing that the 8,000 mg and 2,400 mg doses were similar, the Phase 3 protocol was amended to compare 2,400 mg and 1,200 mg vs. placebo, and 8,000 mg data were converted to a descriptive analysis. Comparisons were between patients randomized to specific casirivimab with imdevimab doses and patients concurrently randomized to placebo.

At baseline, the median age was 50 years (with 14% of subjects ages 65 years or older), 52% of the subjects were female, 84% were White, 36% were Hispanic or Latino, and 5% were Black; all subjects had 1 or more risk factors for severe COVID-19. The median duration of symptoms was 3 days; mean viral load was 6.69 $\log_{10}$ copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary endpoint was the proportion of subjects 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 for the Phase 3 analysis, events occurred in 7 (1.0%) subjects treated with 1,200 mg casirivimab with imdevimab compared to 24 (3.2%) subjects concomitantly randomized to placebo, demonstrating a 70.4% reduction in the number of patients with a COVID-19-related hospitalization or all-cause death ($p<0.0024$); events occurred in 18 (1.3%) subjects treated with 2,400 mg casirivimab with imdevimab compared to 62 (4.6%) subjects randomized to placebo, demonstrating a 71.3% reduction compared to placebo (casirivimab with imdevimab 1.3% vs placebo 4.6%, $p<0.0001$). Consistent effects were observed for the individual doses, indicating the absence of a dose effect (See Table 3). Results were consistent across subgroups of patients defined by viral load at baseline or serologic status (See Figure 1). Benefit versus placebo was observed starting at Day 2 (See Figure 2 and Figure 3).

The key secondary endpoint was time to COVID-19 symptom resolution. The median time to symptom improvement, as recorded in a trial-specific daily symptom diary, was 10 days for casirivimab with imdevimab-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 casirivimab with imdevimab resulted in a 4 days shorter median time to COVID-19 symptom resolution compared to placebo-treated subjects. These results were consistent across subgroups of patients defined by viral load at baseline or serologic status (see Figure 4). Symptoms assessed were fever, chills, sore throat, cough, shortness of breath/difficulty breathing, nausea, vomiting, diarrhea, headache, red/watery eyes, body aches, loss of taste/smell, fatigue, loss of appetite, confusion, dizziness, pressure/tight chest, chest pain, stomachache, rash, sneezing, sputum/phlegm, runny nose. Time to COVID-19 symptoms resolution was defined as time from randomization to the first day during which the subject scored 'no symptom' (score of 0) on all of the above symptoms except cough, fatigue, and headache, which could have been 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0).

Table 3: Summary of Key Phase 3 Results from Study R10933-10987-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)	

Overall, most events were COVID-19-related hospitalization. In the placebo group, there were 3 deaths through Day 29 and 2 additional deaths that occurred after Day 29 for a total of 5 deaths through end of study follow-up. There was 1 death in each treatment group. These results were consistent across the subgroups by baseline viral load >10^6 copies/mL or by serostatus (See Figure 1, Figure 2 and Figure 3).

Figure 1:COVID-19-Related Hospitalizations or All-Cause Death through Day 29

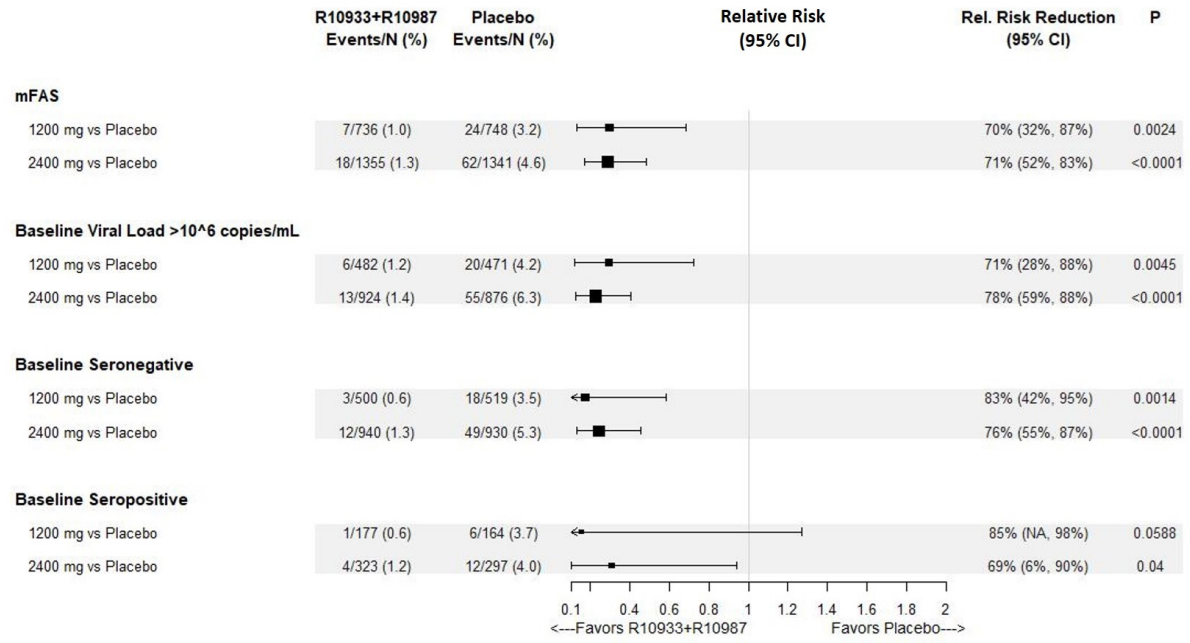


Figure 2:Time to COVID-19-Related Hospitalization or All-Cause Death through Day 29 for REGEN-COV 1,200 mg IV

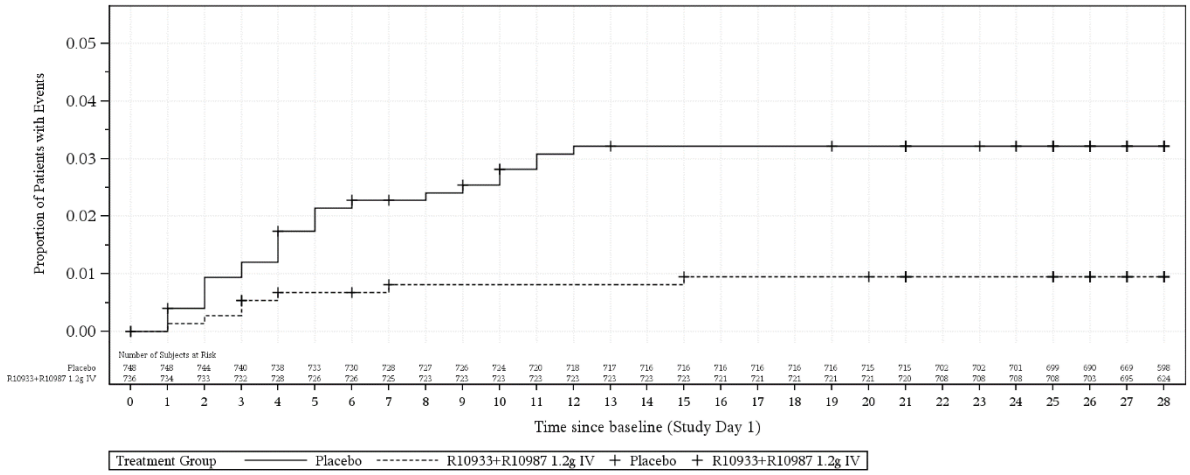


Figure 3:Time to COVID-19-Related Hospitalization or All-Cause Death through Day 29 for REGEN-COV 2,400 mg IV

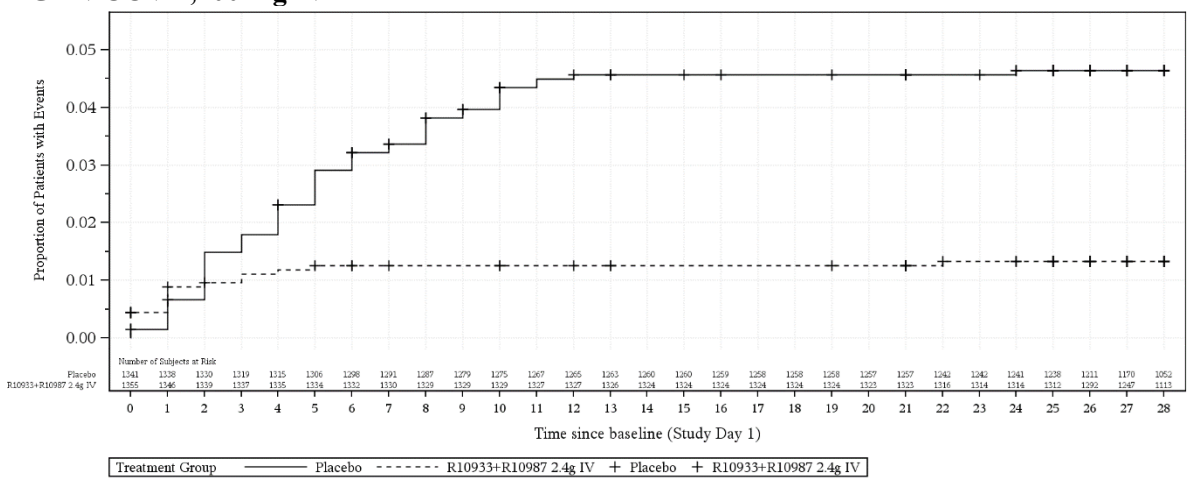
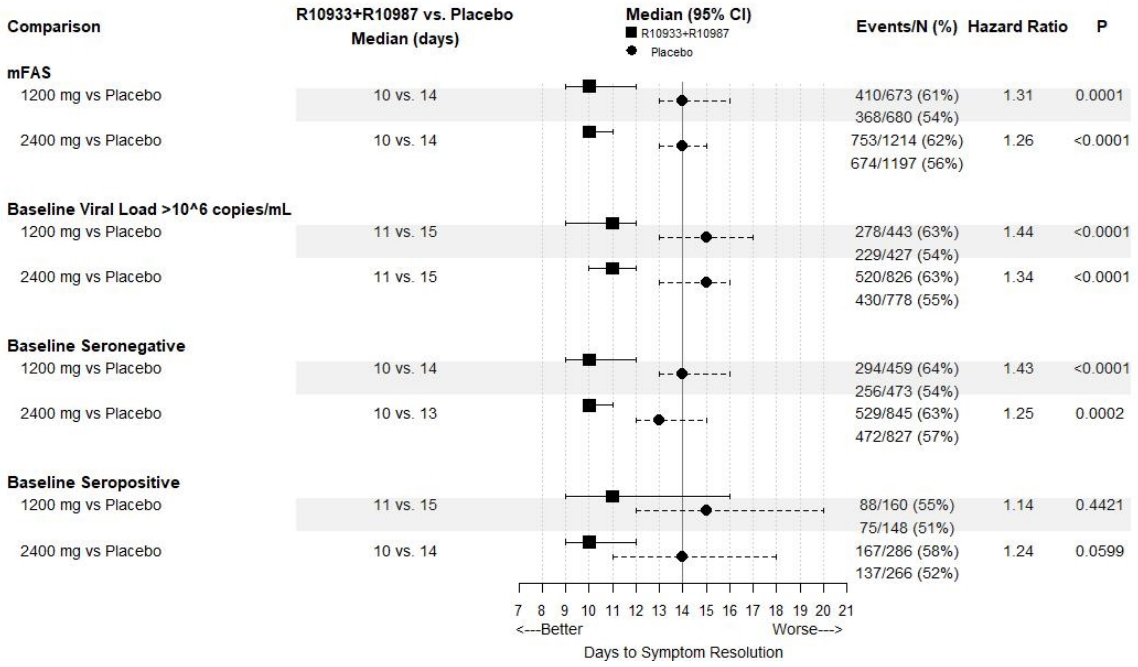
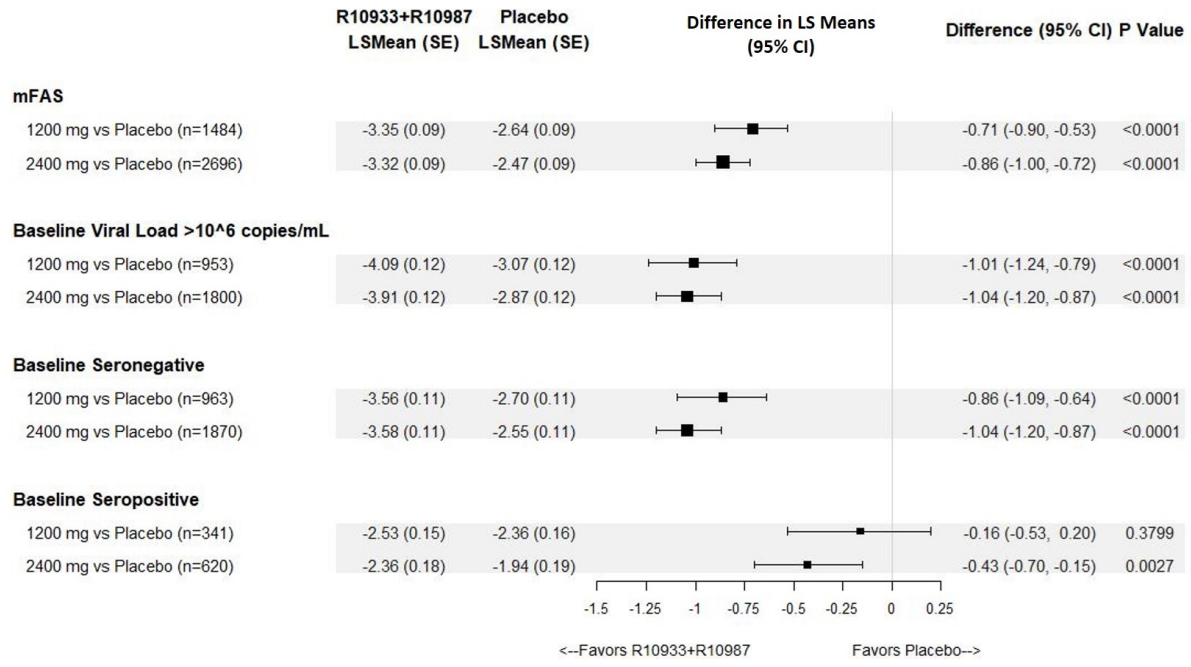


Figure 4:Time to Symptom Resolution



Treatment with casirivimab with 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 log10 copies/mL for 1,200 mg and -0.86 log10 copies/mL for 2,400 mg; p<0.0001). Reductions were observed in the overall mFAS population and in other subgroups, including those with baseline viral load $>10^6$ copies/mL or who were seronegative at baseline. Consistent effects were observed for the individual doses, indicating the absence of a dose effect. Figure 5 shows the mean change from baseline in SARS-COV-2 viral load at Day 7.

Figure 5: Change from Baseline in SARS COV 2 Viral Load (log_{10} copies/mL) at Day 7



The results from the Phase 3 portion of R10933-10987-COV-2067 confirm the efficacy of casirivimab with imdevimab initially observed in the Phase 1/2 analyses.

Phase 1/2 Data from R10933-10987-COV-2067

The efficacy of casirivimab and imdevimab in 799 outpatient adults with COVID-19 was evaluated in a randomized, double-blinded, placebo-controlled Phase 1/2 clinical trial, Study 1 (NCT04425629). Patients were randomized in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2400 mg of the combination of casirivimab and imdevimab (1200 mg of each), 8000 mg of the combination of casirivimab and imdevimab (4000 mg of each), or placebo (n=266, n=267, n=266, respectively). To be eligible for enrollment, subjects had to have laboratory-confirmed SARS-CoV-2 infection, COVID-19 symptom onset ≤ 7 days from randomization, maintain O2 saturation ≥93% breathing room air, not have prior or current use of putative COVID-19 treatments (e.g. convalescent plasma, systemic corticosteroids or remdesivir) and not have been previously or currently hospitalised for treatment of COVID-19.

The study duration was 28 days for each patient. Throughout the study nasopharyngeal (NP) swab samples were collected; information about any medically attended visits related to COVID-19 was also collected.

An initial descriptive analysis on virologic endpoints was conducted on the first 275 patients (Analysis Group 1). To independently replicate the descriptive analyses conducted in the first 275 patients, the primary virologic analyses (see Table 5) were conducted in the next 524 patients (Analysis Group 2). The primary clinical analyses were conducted in the entire 799 patient population. (Analysis Group 1/2).

The demographics and baseline characteristics of these 3 analysis groups are provided in Table 4 below.

Table 4: Demographics and Baseline Characteristics in Study 1

Parameter	Analysis Group 1 n=275	Analysis Group 2 n=524	Analysis Group 1/2 n=799
Mean age years (range)	44 (18-81)	41 (18-89)	42 (18-89)
% over 50 years	32	28	29
% over 65 years	7	7	7
% Female	51	54	53
% White	82	87	85
% Black	13	7	9
% Asian	1	2	2
% Hispanic or Latino ethnicity	56	48	50
% High Risk [a] (≥1 risk factors for severe COVID-19)	64	59	61
% Obese	42	35	37
Median duration of symptoms (days)	3	3	3
Baseline Virologic Parameter			
% Seronegative	41	56	51
Mean log10 copies/mL	6.60	6.34	6.41
% Seropositive	45	34	38
Mean log10	3.30	3.49	3.43

copies/mL			
% Other	14	11	11

[a] The Study 1 defined high risk patients with 1 or more of the following risk factors: Age >50 years; BMI > 30 kg/m2 collected via vital signs CRF; Cardiovascular disease, including hypertension; Chronic kidney disease, including those on dialysis; Chronic lung disease, including asthma; Chronic metabolic disease, including diabetes; Chronic liver disease; and Immunosuppressed, based on investigator's assessment.

Virologic endpoints in Analysis Group 1 were descriptive and were prospectively tested in a hierarchal manner in Analysis Group 2; the hierarchy continued to test clinical endpoints in Analysis Group 1/2.

For all efficacy endpoints, analyses were conducted in a modified full analysis set (mFAS) defined as subjects who had a positive reverse transcription quantitative polymerase chain reaction (RT-qPCR) test at baseline. In Analysis Group 2, the primary virologic endpoint was the reduction in daily viral load (log10 copies/mL) from baseline through day 7 (measured as a mean time-weighted-average daily change). The key clinical endpoint (Analysis Group 1/2) was the proportion of patients who tested RT-qPCR positive at baseline requiring 1 or more medically attended visits (MAVs) for progression of COVID-19. See Table 5 for results tested hierarchically in Analysis Group 2 & Analysis Group 1/2, with side by side descriptive results of Analysis Group 1.

The descriptive virologic endpoints in Analysis Group 1 were hierarchically tested and confirmed in Analysis Group 2 (see Table 5). There was significant reduction in viral load among all patients treated with casirivimab and imdevimab, as measured in NP samples by quantitative RT-qPCR through day 7, see Figure 1. The largest reduction in viral load were seen among patients with high viral load at baseline (> 10^6 or > 10^7 copies/mL) and among patients who were seronegative at baseline, see Figure 7.

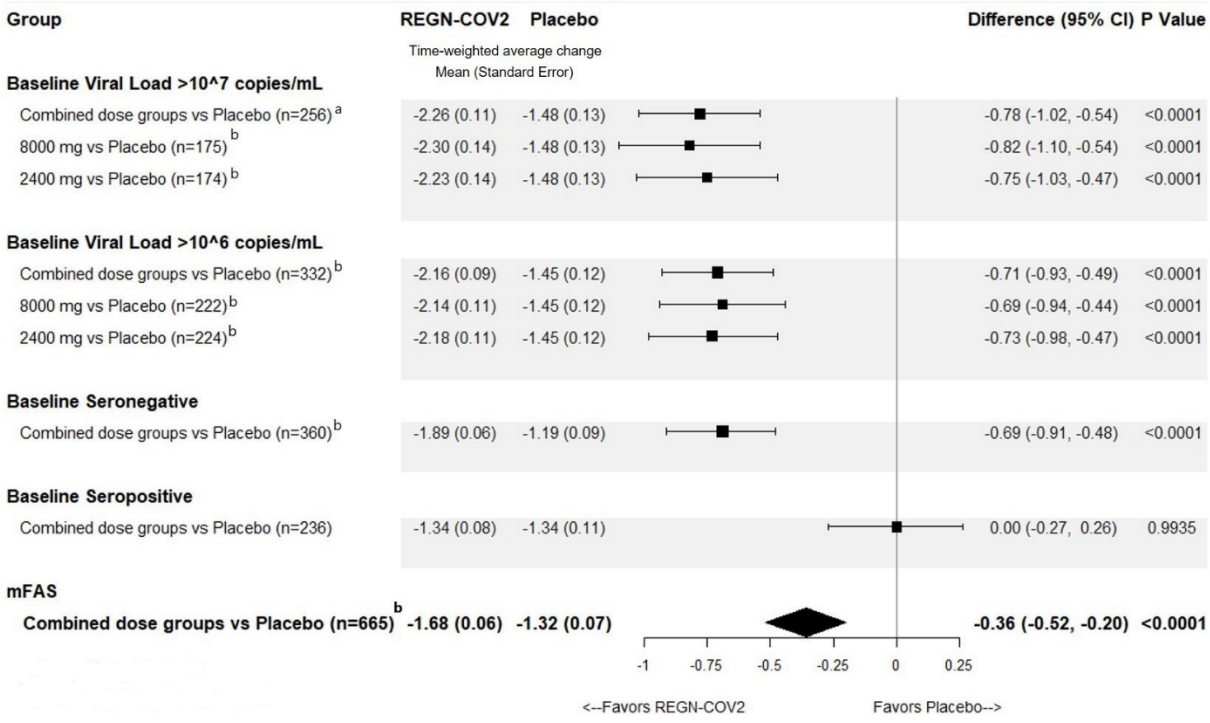
Table 5: Hierarchy for Analysis Group 2 and Analysis Group 1/2

	Analysis Group 1 n=228	**Analysis Group 2 n=437**
1. TWA daily change from baseline (D1) viral load through D7 in the mFAS population with baseline viral load>10^7 copies/mL for the combined dose group vs placebo	Diff from Placebo (p value): -1.21 (0.0001)	Diff from Placebo (p value): -0.68 (<0.0001)
2. TWA daily change from baseline (D1) viral load through D7 in the mFAS population with baseline viral load>10^6 copies/mL for the combined dose group vs placebo	-0.95 (0.0003)	-0.65 (<0.0001)
3. TWA daily change from baseline (D1) viral load through D7 in seronegative mFAS for the combined dose group vs placebo	-0.56 (0.0165)	-0.73 (<0.0001)
4. TWA daily change from baseline (D1) viral load through D7 in mFAS for the combined dose group vs placebo	-0.41 (0.0089)	-0.36 (0.0003)
5. TWA daily change from baseline (D1) viral load through D7 in the mFAS population with baseline viral load>10^7 copies/mL for the 8000 mg dose group vs placebo	-1.32 (0.0002)	-0.68 (<0.0001)
6. TWA daily change from baseline (D1) viral load through D7 in the mFAS population with baseline viral load>10^7 copies/mL for the 2400 mg dose group vs placebo	-1.03 (0.0061)	-0.68 (<0.0001)
7. TWA daily change from baseline (D1) viral load through D7 in the mFAS population with baseline viral load>10^6 copies/mL for the 8000 mg dose group vs placebo	-1.14 (0.0002)	-0.58 (<0.0001)

8. TWA daily change from baseline (D1) viral load through D7 in the mFAS population with baseline viral load>10^6 copies/mL for the 2400 mg dose group vs placebo	-0.81 (0.0063)	-0.73 (<0.0001)
	Analysis Group 1/2 n=665	
9. Proportion of patients with MAVs through D29 in the mFAS for the combined dose group vs placebo (patients 1-799)	Combined Treatment: 12/434 (2.8%) Placebo: 15/231 (6.5%) P=0.0240	
10. Proportion of patients with a subset of MAVs (hospitalisation, ER visit, or urgent care visit) through D29 in the mFAS for the combined dose group vs placebo (patients 1-799)	Combined Treatment: 10/434 (2.3%) Placebo: 10/231 (4.3%) P=0.1575	

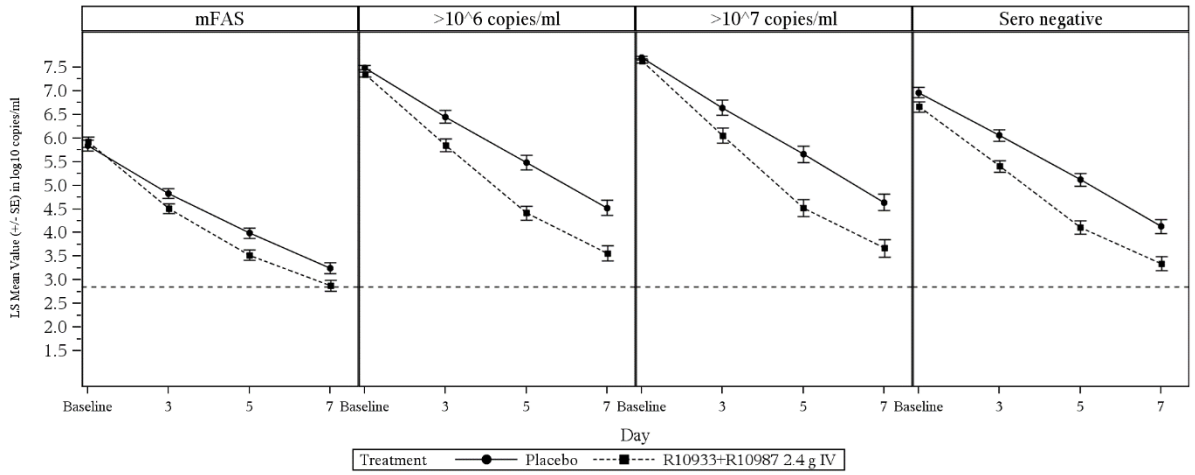
Analysis Group 1 descriptive statistics (nominal p-values) were not included in the hypothesis testing hierarchy but are provided for side by side comparison.

Figure 6: Reduction in Time-Weighted Average Daily Viral Load (log10 copies/mL) through Day 7 (mFAS, Analysis Group 1/2)



[a] Primary Virologic Endpoint
[b] Hierarchically Tested Pre-specified Endpoint
Seronegative was defined as no measurable anti-spike IgG, anti-spike IgA, and anti-nucleocapsid IgG and seropositive was defined as measurable anti-spike IgG, anti-spike IgA, and/or anti-nucleocapsid IgG.

Figure 7: Viral Load Value in Log_{10} Scale at Each Visit through Day 7 in Nasopharyngeal Samples (mFAS, Analysis Group 1/2)



While viral load was used to define the primary endpoint in this Phase 2 trial, clinical data demonstrating that casirivimab and imdevimab may be effective came from the predefined secondary endpoint was medically attended visits. Medically attended visits comprised hospitalisations, emergency room visits, urgent care visits, or telehealth/physician office visits. A lower proportion of patients treated with casirivimab and imdevimab had MAVs as well as COVID-19 related hospitalisation and ER visits compared to placebo, see Table 6. Results for the endpoint MAV were suggestive of a relatively flat dose-response relationship. The absolute risk reduction for casirivimab and imdevimab compared to placebo is greater in subjects at higher risk of hospitalisation according to the high-risk criteria (Table 7).

Table 6: Medically attended Visits in All Patients, mFAS, Analysis Group 1/2

Treatment	N	Events	Proportion of patients
Events of Medically Attended Visits			
Placebo	231	15	6.5%
2400 mg casirivimab and imdevimab	215	6	2.8%
8000 mg casirivimab and imdevimab	219	6	2.7%
All casirivimab and imdevimab doses	434	12	2.8%
Events of Hospitalisation or Emergency Room Visits			
Placebo	231	10	4.3%
2400 mg casirivimab and imdevimab	215	4	1.9%
8000 mg casirivimab and imdevimab	219	4	1.8%
All casirivimab and imdevimab doses	434	8	1.8%

Analysis Group 1/2 is defined as the 665 patients enrolled in phase 1 and phase 2 of COV-2067.

Table 7: Medically Attended Visits in Patients at Risk, mFAS, Analysis Group 1/2

Treatment	N	Events	Proportion of patients
Events of Medically Attended Visits			
Placebo	142	13	9.2%
2400 mg casirivimab and imdevimab	134	3	2.2%
8000 mg casirivimab and imdevimab	132	4	3%
All casirivimab and imdevimab doses	266	7	2.6%
Events of Hospitalisation or Emergency Room Visits			
Placebo	142	9	6.3%
2400 mg casirivimab and imdevimab	134	2	1.5%
8000 mg casirivimab and imdevimab	132	3	2.3%
All casirivimab and imdevimab doses	266	5	1.9%

Analysis Group 1/2 is defined as the 665 patients enrolled in phase 1 and phase 2 of COV-2067.

Paediatric population

No results are available to date (see section 4.2 and 5.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of casirivimab and imdevimab in 45 ambulatory patients with COVID-19 aged 18 to 72 years are linear and dose proportional over the range of 1200 mg casirivimab and 1200 mg imdevimab to 4000 mg casirivimab and 4000 mg imdevimab when given in combination as a single intravenous (IV) infusion. Pharmacokinetic parameters for the individual antibodies following a 2400 mg IV dose of casirivimab and imdevimab (1200 mg per antibody) are provided in Table 8.

Table 8: Pharmacokinetic Parameters of Casirivimab and Imdevimab in Outpatients with COVID-19

Pharmacokinetic Parameter[a]	Casirivimab 1200 mg[b]	Imdevimab 1200 mg[b]
Mean (SD) C_{max} (mg/L)	325 (214)	364 (265)
Mean (SD) AUC_{0-28} (mg•day/L)	3393 (1887)	3492 (2916)
Mean (SD) C_{28} (mg/L)[c]	68.0 (45.2)	64.9 (53.9)

[a] n=22 for Cmax; n=16 and 17 for casirivimab and imdevimab AUC0-28, respectively; n=17 for C28

[b] A total dose of 2400 mg of casirivimab and imdevimab was administered; 1200 mg of casirivimab and 1200 mg of imdevimab, in a 1:1 ratio

[c] Observed concentration 28 days after dosing

The metabolic pathways of casirivimab and imdevimab have not been characterized. As human monoclonal IgG1 antibodies, both casirivimab and imdevimab are expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Specific Populations

The effects of age, renal impairment, or hepatic impairment on the pharmacokinetics of casirivimab and imdevimab are unknown. The recommended dosing regimen is expected to result in comparable serum exposures of casirivimab and imdevimab in patients 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in Trial R10933-10987-COV-2067. Renal impairment is not expected to impact the pharmacokinetics of casirivimab and imdevimab components, since mAbs with molecular weight >50 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the pharmacokinetics of casirivimab and imdevimab.

Elderly patients
There are limited data on the safety and efficacy of patients aged 65 years and above. Of the 4,567 patients with SARS-CoV-2 infection randomized in an ambulatory clinical trial (R10933-10987-COV-2067), 14% were 65 years or older, and 4% were 75 years of age or older. The difference in PK of casirivimab and imdevimab in geriatric patients compared to younger patients is unknown.

5.3 Preclinical safety data

The nonclinical toxicology profiles of casirivimab and imdevimab have been characterized through the conduct of a repeat-dose toxicology study in cynomolgus monkeys. These mAbs were administered weekly, alone (50 mg/kg) via IV bolus injection, and in combination (up to 150 mg/kg/antibody) via IV or SC injection. Once weekly administration of casirivimab, imdevimab, and casirivimab and imdevimab, were well tolerated at all dose levels, with no drug-related or adverse effects evident during the 4-week dosing period or at the time of necropsy. An ex vivo tissue cross-reactivity study was conducted using panels of normal human and cynomolgus monkey tissues. There was no off-target binding of casirivimab or imdevimab in any of the human or monkey tissues evaluated, which was anticipated as both mAbs bind an exogenous protein.

Carcinogenicity, genotoxicity, reproductive toxicology, and fertility studies have not been conducted with casirivimab and imdevimab.

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: 24 months

After opening: Once opened, the medicinal product should be diluted and infused immediately.

After dilution: the diluted solution may be stored for up to 4 hours at room temperature (up to 25°C) or refrigerated between 2°C to 8°C for up to 36 hours.

6.4. Special precautions for storage

Store in a refrigerator at 2°C to 8°C in the original carton to protect from light.

Do not freeze.

Do not shake.

6.5. Nature and contents of container

Casirivimab and imdevimab are provided in clear Type 1 glass vials in 20 mL or 6 mL vials.

Each carton contains 2 vials per package:

1 vial of 1332 mg/11.1 mL of casirivimab and 1 vial of 1332 mg/11.1 mL imdevimab or
1 vial of 300 mg/2.5 mL of casirivimab and 1 vial of 300 mg/2.5 mL imdevimab.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Instructions for Dilution
Casirivimab and imdevimab are for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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 concentrates must be discarded, and new vials used.
   - The concentrates in each vial should be clear to slightly opalescent, colorless to pale yellow.
3. Obtain a prefilled IV infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection.
   - Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial(s) using separate syringes for each withdrawal and inject all 20 mL into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see Table 9). Discard any product remaining in the vial.
4. Gently invert infusion bag by hand approximately 10 times to mix. Do not shake.
5. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.
   - If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 9: Recommended Dosing, Dilution and Administration Instructions for 1,200 mg Casirivimab with 1,200 mg Imdevimab for Intravenous Infusion

Casirivimab with Imdevimab 2,400 mg Dose[a]. Add: • **10 mL of casirivimab (use 1 vial of 11.1 mL OR 4 vials of 2.5 mL) and** • **10 mL of imdevimab (use 1 vial of 11.1 mL OR 4 vials of 2.5 mL)** **for a total of 20 mL into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below[b]**		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL	210 mL/hr	20 minutes
100 mL	360 mL/hr	20 minutes
150 mL	510 mL/hr	20 minutes
250 mL	540 mL/hr	30 minutes

[a]1,200 mg of casirivimab and 1,200 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.
[b]After infusion is complete, flush with 0.9% Sodium Chloride Injection.

Administration

Casirivimab with imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- 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-micron polyethersulfone (PES) filter (see Table 9). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- 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 is not known.
- After infusion is complete, flush the tubing with 0.9% Sodium Chloride Injection to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

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

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD Month YYYY

10. DATE OF REVISION OF THE TEXT