ANNEX I (corr. 2) [1, 2]

CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION, PATIENTS TARGETED AND CONDITIONS FOR SAFETY MONITORING ADRESSED TO MEMBER STATES

FOR

UNAUTHORISED PRODUCT

AVAILABLE FOR USE

[1] A correction was made regarding the shelf life of the medicinal product. In addition, some formatting changes were introduced (3 March 2021).
[2] A correction was made to change the tables and figures references. In addition, some formatting changes were introduced. (24 March 2021).

This medicine is subject to additional monitoring. This enables new safety information to be identified quickly. Healthcare Professionals are asked to report any suspected adverse reactions. For information on reporting side effects, see section 6.

1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for Use: TBC**
- **Active substance(s): casirivimab and imdevimab (REGN-COV2)**
- **Pharmaceutical form: Concentrate for solution for infusion**
- **Route of administration: Intravenous infusion**
- **Strength: 120 mg/mL of casirivimab and 120 mg/mL of imdevimab**

2. NAME AND CONTACT DETAILS OF THE COMPANY

Name: Regeneron Ireland DAC

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3. TARGET POPULATION

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 prescriber'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.

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to medical prescription.

5. CONDITIONS OF USE

Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis.

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.

5.1 Posology

- **Dosing recommendations**

The recommended dose is 1200 mg of casirivimab and 1200 mg of imdevimab administered as a single intravenous infusion.

- **Treatment duration and monitoring**

Administer 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.

- **Specific Populations**

Paediatric use
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.

Geriatric use
No dose adjustment is required in patients ≥ 65 years of age.

Renal Impairment
No dosage adjustment is recommended in patients with renal impairment.

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.

- **Method of administration**

REGN-COV2 is for administration by intravenous infusion.

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, colourless 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.
4. Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial using two separate syringes (see Table 1) and inject all 20 mL into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see Table 1). Discard any product remaining in the vial.
5. Gently invert infusion bag by hand approximately 10 times to mix. Do not shake.
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.
    - If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C for no more than 36 hours or at room temperature up to 25°C 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 1: Recommended Dosing, Dilution and Administration Instructions for Casirivimab with Imdevimab for IV 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 casirivimab and 1,200 mg 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

5.2 Contraindications

Hypersensitivity to casirivimab or imdevimab or to any of the excipients.

5.3 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 fever, difficulty breathing, reduced oxygen saturation, chills, nausea, arrythmia (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.

5.4 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
Concomitant administration of REGN-COV2 with COVID-19 vaccines has not been studied.

5.5 Pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of REGN-COV2 in pregnant women. Animal reproductive toxicity studies are not available, however, in a tissue cross-reactivity study with casirivimab and imdevimab using human foetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, REGN-COV2 has the potential to be transferred from the mother to the developing foetus. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing foetus. REGN-COV2 should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus considering all associated health factors.

Lactation
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. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decrease to low concentrations soon afterwards. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for REGN-COV2 and any potential adverse effects on the breastfed child from REGN-COV2 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.

5.6 Incompatibilities

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

5.7 Overdose

There is no human experience of acute overdosage with REGN-COV2. Doses up to 8,000 mg (4,000 mg each of casirivimab and imdevimab, greater than 3 times the 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 REGN-COV2.

List of excipients:
L-histidine
L-histidine monohydrochloride monohydrate
polysorbate 80
sucrose
Water for Injection

5.8 Shelf life
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.

Shelf life for unopened vials is 12 months.

5.9 Storage conditions

Store in a refrigerator at 2°C to 8°C in the original carton to protect from light.
Do not freeze.
Do not shake.

5.10 Special precautions for disposal

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

6. OTHER INFORMATION

- **Undesirable effects**

Summary of the safety profile
Overall, more than 2,100 subjects have been exposed to intravenous casirivimab and imdevimab in clinical trials including healthy volunteers and patients.

The safety of casirivimab and imdevimab are based on analysis of data from study R10933-10987-COV-2067 a randomized, double-blind, placebo-controlled Phase I/II clinical trial in ambulatory 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. Subjects 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). The adverse events collected were 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 authorized at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).

Tabulated summary of adverse reactions
Table 2 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 2: 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'.

Description of selected adverse reactions
Hypersensitivity Including Anaphylaxis and Infusion-related Reactions
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.

In two subjects receiving the 8,000 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).

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

- **Summary of relevant pharmacological properties**

Mechanism of action
REGN-COV2 is 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. REGN-COV2 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 REGN-COV2 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 REGN-COV2 has been assessed in rhesus macaques and Syrian golden hamsters. Therapeutic administration of REGN-COV2 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 REGN-COV2 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 the casirivimab + imdevimab combination.

Escape variants were identified following 2 passages in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following 2 passages in the presence of the casirivimab + imdevimab combination. Variants which showed reduced susceptibility to casirivimab individually included 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 individually included K444N (>755-fold), K444Q (>548-fold), K444T (>1033-fold), and V445A (>548-fold) substitutions. The combination of casirivimab + imdevimab showed reduced susceptibility to K444T (6-fold) and V445A (5-fold) variants.

In neutralization assays using VSV pseudotyped with 39 different spike protein variants from circulating SARS-CoV-2 viruses casirivimab individually had reduced neutralization of Q409E (4-fold), G476S (5-fold) and S494P (5-fold) variants, and imdevimab individually had reduced neutralization of the N439K (463-fold) variant. The casirivimab + imdevimab combination retained activity against all variants tested.

The impact of individual mutations identified in either the United Kingdom B.1.1.7 variant or South African B.1.351 variant on neutralization potency of the individual mAbs, and the casirivimab + imdevimab combination in the VSV-based pseudovirus neutralization assay were evaluated. The casirivimab + imdevimab combination retained its highly potent neutralizing capacity against the B.1.1.7 and the B.1.351 variants. Both individual mAbs retained their potency against the B.1.1.7 variant. Imdevimab retained its potency against the B.1.351 variant.

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 + imdevimab combination groups, and one at Day 25 in a subject from the 8,000 mg casirivimab + imdevimab combination 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 and the casirivimab + imdevimab combination.

It is possible that resistance-associated variants to the casirivimab + imdevimab combination 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.

- **Summary of relevant Clinical properties**

The efficacy of REGN-COV2 in 799 outpatient adults with COVID-19 was evaluated in a randomized, double-blinded, placebo-controlled 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 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 3 below.

Table 3: 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

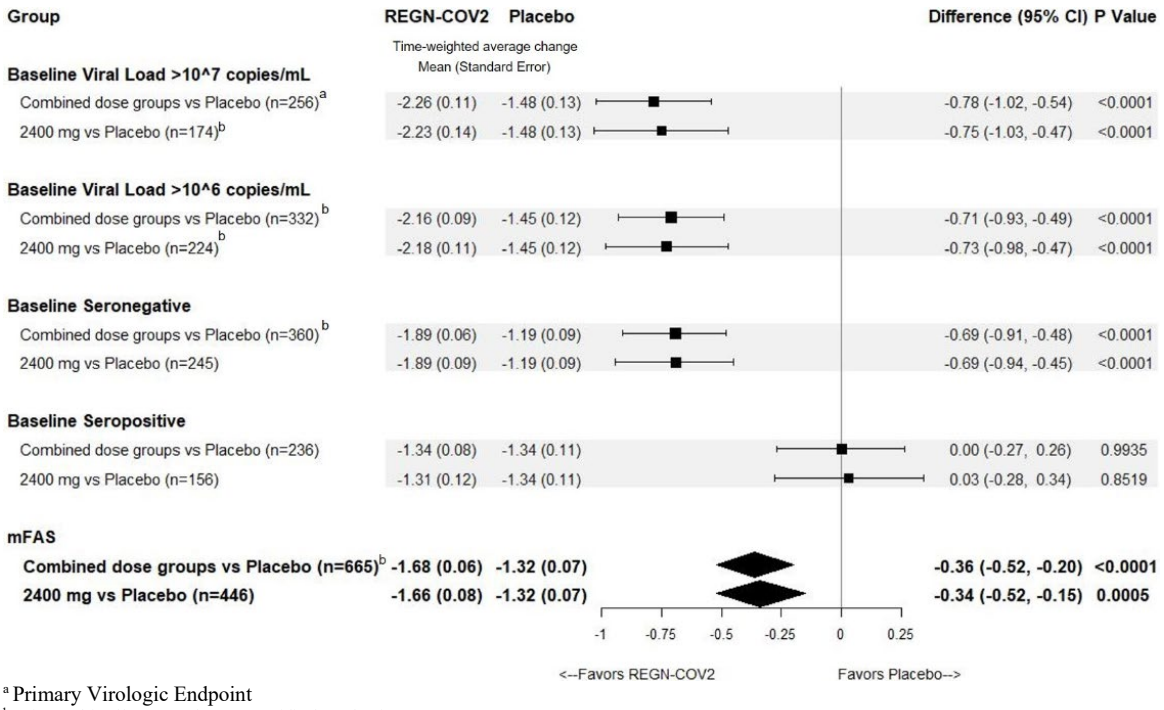
Parameter	Analysis Group 1 n=275	Analysis Group 2 n=524	Analysis Group 1/2 n=799
% Asian	1	2	2
% Hispanic or Latino ethnicity	56	48	50
% High Risk [a] (≥1 risk factors for severe COVID-19)	64	59	61
% Obese	42	35	37
Median duration of symptoms (days)	3	3	3
Baseline Virologic Parameter			
% Seronegative	41	56	51
Mean log10 copies/mL	6.60	6.34	6.41
% Seropositive	45	34	38
Mean log10 copies/mL	3.30	3.49	3.43
% 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.

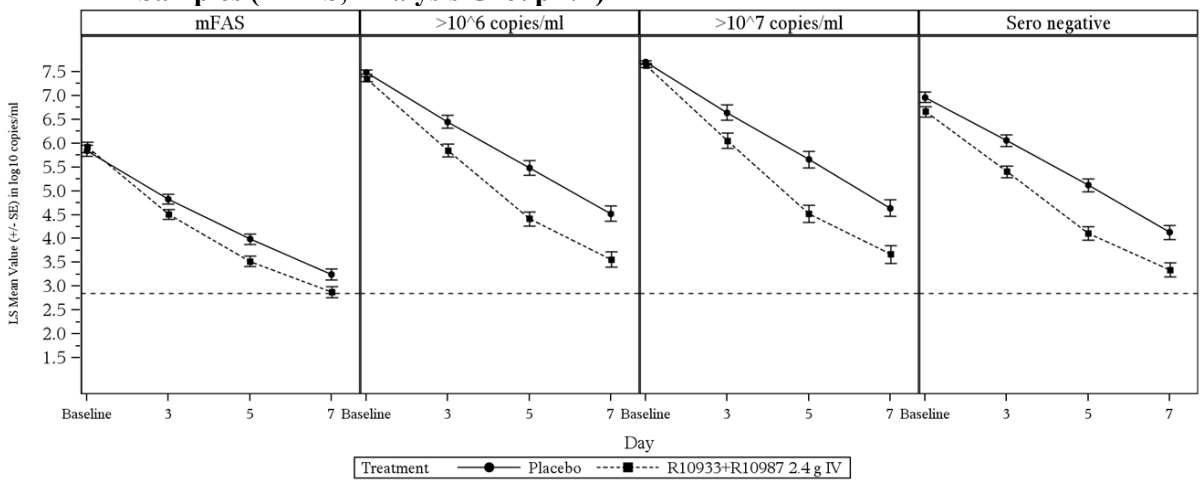
The descriptive virologic endpoints in Analysis Group 1 were hierarchically tested and confirmed in Analysis Group 2. There was significant reduction in viral load among all patients treated with REGN-COV2, as measured in NP samples by quantitative RT-qPCR through day 7, see Figure 1. The largest reduction 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 2.

Figure 1: 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 2: Viral Load Value in Log10 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, important clinical evidence demonstrating that REGN-COV2 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 REGN-COV2 had MAVs as well as COVID-19 related hospitalisation and ER visits compared to placebo, see Table 4. Results for this endpoint were suggestive of a relatively flat dose-response relationship. The absolute risk reduction for REGN-COV2 compared to placebo is greater in subjects at higher risk of hospitalisation according to the high-risk criteria and in those that are seronegative at baseline (Table 5 – Table 8).

Table 4: Medically attended Visits in All Patients, mFAS, Analysis Group 1/2

Treatment	N	Events	Proportion of patients	Risk Difference	95% CI
Events of Medically Attended Visits					
Placebo	231	15	6.5%		
2400 mg REGN-COV2	215	6	2.8%	-3.7%	-8.0%, 0.3%
All REGN-COV2 doses	434	12	2.8%	-3.7%	-7.9%, -0.3%
Events of Hospitalisation or Emergency Room Visits					
Placebo	231	10	4.3%		
2400 mg REGN-COV2	215	4	1.9%	-2.5%	-6.2%, 0.9%
All REGN-COV2 doses	434	8	1.8%	-2.5%	-6.1%, 0.2%

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

Table 5: Medically Attended Visits in High Risk Patients, mFAS, Analysis Group 1/2

Treatment	N	Events	Proportion of patients	Risk Difference	95% CI
Events of Medically Attended Visits					
Placebo	142	13	9.2%		
2400 mg REGN-COV2	134	3	2.2%	-6.9%	-13.2%, -1.3%
All REGN-COV2 doses	266	7	2.6%	-6.5%	(-12.7%, -1.6%)
Events of Hospitalisation or Emergency Room Visits					
Placebo	142	9	6.3%		
2400 mg REGN-COV2	134	2	1.5%	-4.8%	-10.4%, -0.1%
All REGN-COV2 doses	266	5	1.9%	-4.5%	-10.0%, -0.5%

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

Table 6: Medically Attended Visits in Patients Not at High Risk, mFAS, Analysis Group 1/2

Treatment	N	Events	Proportion of patients	Risk Difference	95% CI
Events of Medically Attended Visits					
Placebo	89	2	2.2%		
2400 mg REGN-COV2	81	3	3.7%	1.5%	-13.5%, 16.4%
All REGN-COV2 doses	168	5	3.0%	0.7%	-12.1%, 13.5%
Events of Hospitalisation or Emergency Room Visits					
Placebo	89	1	1.1%		
2400 mg REGN-COV2	81	2	2.5%	1.3%	-13.7%, 16.3%
All REGN-COV2 doses	168	3	1.8%	0.7%	-12.2%, 13.5%

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 Seronegative Patients, mFAS, Analysis Group 1/2

Treatment	N	Events	Proportion of patients	Risk Difference	95% CI
Events of Medically Attended Visits					
Placebo	124	12	9.7%		
2400 mg REGN-COV2	121	4	3.3%	-6.4%	-13.4%, -0.1%
All REGN-COV2 doses	236	8	3.4%	-6.3%	-13.2%, -0.8%
Events of Hospitalisation or Emergency Room Visits					
Placebo	124	7	5.6%		
2400 mg REGN-COV2	121	3	2.5%	-3.2%	-15.7%, 9.3%
All REGN-COV2 doses	236	6	2.5%	-3.1%	-13.9%, 7.8%

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

Table 8: Medically Attended Visits in Seropositive Patients, mFAS, Analysis Group 1/2

Treatment	N	Events	Proportion of patients	Risk Difference	95% CI
Events of Medically Attended Visits					
Placebo	83	2	2.4%		
2400 mg REGN-COV2	73	2	2.7%	0.3%	-6.1%, 7.4%
All REGN-COV2 doses	153	3	2.0%	-0.4%	-6.8%, 4.0%
Events of Hospitalisation or Emergency Room Visits					
Placebo	83	2	2.4%		
2400 mg REGN-COV2	73	1	1.4%	-1.0%	-16.6%, 14.6%
All REGN-COV2 doses	153	1	0.7%	-1.8%	-15.0%, 11.6%

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

The median time to symptom improvement as recorded in a trial specific daily symptom diary was 5 days for REGN-COV2-treated patients with 1 or more risk factors, as compared with 7 days for placebo-treated patients in Analysis Group 1/2. The median time to symptom improvement as recorded in a trial specific daily symptom diary was 5 days for REGN-COV2-treated patients with 2 or more risk factors, as compared with 11 days for placebo-treated subjects. Symptoms assessed were feverish, chills, sore throat, cough, shortness of breath/difficulty breathing, nausea, vomiting, diarrhoea, headache, red/watery eyes, body aches, loss of taste/smell, fatigue, loss of appetite, confusion, dizziness, pressure/tight chest, chest pain, stomach ache, rash, sneezing, sputum/phlegm, runny nose. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent.

7. CONDITIONS FOR SAFETY MONITORING

This medicine is subject to additional monitoring. This enables new safety information to be identified quickly. Healthcare Professionals are asked to report any suspected adverse reactions. For information on reporting side effects, see section 6.

8. DATE OF CHMP OPINION