Emergency Use Authorization (EUA) for
casirivimab and imdevimab
Center for Drug Evaluation and Research (CDER) Review

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	000091
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Regeneron Pharmaceuticals, Inc. Yunji Kim, PharmD Director, Regulatory Affairs Regeneron Pharmaceuticals, Inc. Email: yunji.kim@regeneron.com
Manufacturer	Regeneron Pharmaceuticals, Inc.
Submission Date(s)	March 23, 2021 (eCTD #0077) March 26, 2021 (eCTD #0080) April 23, 2021 eCTD #0098)
Receipt Date(s)	March 23, 2021 (eCTD #0077) March 26, 2021 (eCTD #0080) April 23, 2021 (eCTD #0098)
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Proprietary Name	REGEN-COV
Established Name/Other names used during development	casirivimab (REGN10933) and imdevimab (REGN10987)
Dosage Forms/Strengths	**Currently Authorized Dose:** 1200 mg intravenous (IV) casirivimab and 1200 mg IV imdevimab
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1 monoclonal antibodies (mAbs)
Intended Use or Need for EUA	Mild to moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization • **Proposed dose:** 600 mg casirivimab IVand 600 mg imdevimab IV • **Proposed alternative route of administration:** Subcutaneous administration of 600 mg casirivimab and 600 mg imdevimab, when IV infusion is not feasible and would lead to delay in treatment

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I. Summary

This review summarizes the Applicant's proposals and the Division's review and assessments for the following:

- Revision of the authorized dose for EUA 91.
- Authorization of subcutaneous dosing as an alternative in addition to the currently authorized intravenous administration for the treatment of high risk patients with mild to moderate COVID-19.
- Authorization of the coformulation product in a single vial.

Currently, EUA 91 authorizes use of REGEN-COV for the treatment of mild to moderate COVID-19 in adult and pediatric patients (12 years of age older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. The authorized dose is 2400 mg of REGEN-COV consisting of 1200 mg of casirivimab and 1200 mg of imdevimab administered together as a single intravenous (IV) infusion. The Applicant has proposed revision of the authorized dose, as follows:

- 1200 mg of REGEN-COV (600 mg of casirivimab and 600 mg of imdevimab)

1) Authorization of 1200 mg dose (600 mg of casirivimab and 600 mg of imdevimab) for treatment

In support of their proposal, the Applicant submitted topline results from phase 3 analyses of study COV-2067 (NCT04425629). Based on review of available data, we have determined that the EUA criteria are met for authorization of the 1200 mg dose of REGEN-COV (600 mg of casirivimab and 600 mg of imdevimab) for the following reasons:

- A clinically and statistically significant reduction in COVID-19-related hospitalization and all-cause deaths through study day 29 was observed with 1200 mg REGEN-COV compared to the concurrent placebo group in symptomatic patients with at least one CDC high risk factor for severe COVID-19. The magnitude of clinical response, approximately 70% reduction in hospitalization and death, was similar in the 1200 mg vs placebo analysis and the 2400 mg vs placebo analysis. Similar responses were also observed with the 1200 mg dose compared to the 2400 mg dose for secondary endpoints of time to resolution of COVID-19 symptoms, and mean change in viral load from baseline to day 7.
- The safety profile was generally similar in the two dose groups. The major safety concerns were infusion-related reactions and hypersensitivity reactions, including anaphylaxis.

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- Given the timing of the phase 3 trial, we anticipate that a small proportion of phase 3 patients may have been infected with currently circulating SARS-CoV-2 variants of concern or variants of interest, including B.1.526 (New York origin). Genotypic data from phase 3 studies and nonclinical neutralization results from authentic virus experiments with variant viruses are not available at the present time. Based on available pseudotyped virus-like particle (VLP) neutralization data and estimated concentrations of casirivimab and imdevimab in plasma and lung, the 1200 mg dose of REGEN-COV is expected to retain clinical efficacy against currently circulating variants of concern and variants of interest.

Based on the totality of the available scientific evidence, we recommend authorization of the 1200 mg dose (600 mg of casirivimab and 600 mg of imdevimab).[1]

2) *Authorization of subcutaneous route of administration for treatment*
In support of the above proposal, the Applicant submitted PK data from the 1200 mg dose administered intravenously and subcutaneously observed across studies COV-2067 and COV-2069. Data from the phase 2 dose-ranging study, COV-20145, provided viral load reductions at all available time points on or before Day 7, which indicate a comparable viral load reduction for the 1200 mg IV and 1200 mg subcutaneous dose. Based on the totality of the available evidence including safety findings with subcutaneous administration, we support authorization of the 1200 mg subcutaneous dose (600 mg of casirivimab and 600 mg of imdevimab) as an alternative when IV administration is not feasible and would lead to a delay in treatment.

3) *Authorization of co-formulation product*
The Applicant submitted CMC information to introduce a co-formulation presentation which consists of a single vial containing casirivimab and imdevimab drug products. Each co-formulation vial provides a single treatment dose of 600 mg of casirivimab and 600 mg of imdevimab for the treatment of adult and pediatric patients (12 years of age older weighing at least 40 kg). Product quality, manufacturing, and control information as well as the proposed carton and container labeling support authorization of the co-formulated drug product.

4) *Revision of the Indication of Authorized Use*
As the phase 3 primary endpoint in COV-2067 included all-cause death, the Agency revised the Indication statement to specify that authorization is for treatment of patients who are at high risk of progression to severe COVID-19, including hospitalization or death.

[1] Upon re-issuance of the Letter of Authorization reflecting this change in dosing, the 2400 mg dose (1,200 mg of casirivimab and 1,200 mg of imdevimab) will no longer be authorized.

5) *Updates for hypersensitivity and infusion-related reactions*
We recommend updating the description of infusion-related reactions in the EUA Healthcare Provider (HCP) Fact Sheet to include 'vasovagal reactions (e.g., pre-syncope, syncope)' and to specify that hypersensitivity reactions occurring more than 24 hours after the infusion were reported with use under EUA.

II. Revised Authorized Dose

A. Introduction

Topline clinical data from the phase 3 portion of study COV-2067 support this dose revision and form the primary basis of authorization for this EUA amendment. COV-2067 is a phase 1/2/3, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of REGEN-COV in outpatients (non-hospitalized) with SARS-CoV-2 infection. The first 799 symptomatic patients who were randomized were part of a combined phase 1 and 2 analysis. The original EUA issuance, on 11/21/2020, was based on this combined phase 1 and 2 analysis. All symptomatic patients, beginning with the 800th randomized patient, were included in the phase 3 portion of the trial and in the current analysis.

B. Design

In phase 1 and 2, patients were randomized 1:1:1 to 2400 mg IV or 8000 mg IV or placebo arms. As no dose-effect was observed in the combined phase 1 and 2 analysis, the 8000 mg dose arm was discontinued from phase 3. The 2400 mg dose arm was maintained in phase 3. A lower 1200 mg dose arm was introduced as part of protocol amendment 6. Patients were enrolled into 1 of 3 cohorts: cohort 1 (at least 18 years of age, not pregnant at randomization), cohort 2 (less than 18 years of age, not pregnant at randomization), and cohort 3 (pregnant at randomization). In Cohort 1, eligible patients were randomized 1:1:1 to receive a single dose of placebo or casirivimab and imdevimab, as follows:

- 1200 mg IV (600 mg of casirivimab and 600 mg imdevimab)
- 2400 mg IV (1200 mg of casirivimab and 1200 mg imdevimab)
- Placebo IV

Patients with laboratory-confirmed SARS-CoV-2 infection (positive SARS-CoV-2 RT-PCR test) diagnosed ≤72 hours of randomization and with COVID-19 symptoms for <7 days prior to randomization were enrolled. Mild-to-moderate disease was defined as follows: participants had to maintain oxygen saturation ≥93% breathing room air, not have been previously or currently hospitalized for treatment of COVID-19; were experiencing at least one of the following

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symptoms at randomization: fever, cough, shortness of breath. Prior or current use of putative COVID-19 treatments (e.g., corticosteroids, convalescent plasma, or remdesivir) or SARS-CoV-2 vaccination was an exclusion criterion in phase 3. The study treatment was administered on Day 1. Participants were followed for 29 days.

Data from all symptomatic patients in Cohort 1 who enrolled on or before January 17, 2021 in the original and amended phase 3 portion of COV-2067 form the basis for the EUA amendment. At the present time, Cohort 1 is closed to enrollment; while Cohorts 2 and 3 are currently enrolling pediatric and pregnant patients.

A major protocol change in phase 3 included revision of the inclusion/exclusion criteria (protocol amendment 6). Prior to protocol amendment 6, phase 3 enrolled patients with no risk factors or with high risk factors for severe COVID-19. Based on FDA recommendations, the protocol was amended (amendment 6) during phase 3 to restrict enrollment to only patients with at least one risk factor for severe COVID-19, as defined below. These phase 3 protocol-defined risk factors were based on current CDC definitions and are broader than those outlined in the original EUA HCP FS.

Protocol-defined criteria for high risk factors are as follows:

- Age ≥50 years
- Body mass index (BMI) ≥30 kg/m^2
- 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 investigator's assessment. Examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications

Original EUA HCP FS criteria for high risk factors are as follows:

- BMI ≥35 kg/m^2
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease
- Currently receiving immunosuppressive treatment
- ≥65 years
- ≥55 years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR

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- chronic obstructive pulmonary disease/other chronic respiratory disease.

If pre-dose virologic results from the qualitative SARS-CoV-2 RT-PCR test at baseline were missing (i.e., not available), then results from post-dose sample were used to determine the qualitative RT-PCR status at baseline as long as the sample was collected within two hours after starting the study drug infusion.

The primary efficacy endpoint is proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through Day 29. The key secondary endpoints include proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from Day 4 through Day 29 and time to COVID-19 symptom resolution.

The full analysis set (FAS) included all randomized patients in Phase 3 Cohort 1, including those with or without protocol-defined risk factors.

The modified full analysis set (mFAS) was the pre-specified primary efficacy analysis set which included patients in the FAS who had a *positive central-lab-determined RT-qPCR test* from NP swab samples at randomization and *at least one protocol-defined risk factor* for severe COVID-19 at baseline.

To control the overall type I error at 0.05, the primary and key secondary efficacy endpoints were evaluated in mFAS and subgroups in a hierarchical order. In addition, comparisons between REGEN-COV 2400 mg and placebo and between REGN-COV 1200 mg and placebo were based on concurrent enrollment.

C. Demographics and Baseline Characteristics

The key demographic and baseline disease characteristics were generally well balanced in the two REGEN-COV dose groups and the placebo group in the FAS with at least one protocol-defined risk factor, as shown in Table 2. The median age was 50 years with 13% of subjects ages 65 years or older. Approximately half the participants were female. About 36% the participants were Hispanic or Latino and 5% were Black or African American. Approximately 42% of subjects reported at least 1 severe symptom at baseline, 42% reported at least 1 moderate symptom and no severe symptoms, and 15% reported only mild symptoms.

Approximately 25% of participants were seropositive for the SARS-CoV-2 virus at baseline as determined by either positive Euroimmune IgA, Euroimmune IgG, or Abbot Architect IgG assay.

A total of 1484 patients in the mFAS who were concurrently enrolled in the 1200 mg and placebo arms after protocol amendment 6 were included in the 1200 mg

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vs placebo analysis. The 2400 mg vs placebo analysis included 2696 mFAS patients who were concurrently enrolled in the two arms before and after amendment 6. The patient demographics and baseline characteristics for the patients included in the 1200 mg mFAS analysis and 2400 mg mFAS analysis were similar to those for the FAS with at least one protocol-defined risk factor shown in Table 1.

Table 1: Baseline Demographics and Disease Characteristics in COV-2067 (FAS with at least one protocol-defined risk factor)

	Placebo (N=1500)	1200 mg REGN-COV (N=838)	2400 mg REGN-COV (N=1529)	8000 mg REGN-COV (N=700)	Total (N=4567)
Age (median years)	49	48	50	51	50
Age ≥ 50 years	748 (50%)	402 (48%)	790 (52%)	398 (57%)	2338 (51%)
Age ≥ 65 years	160 (11%)	104 (12%)	235 (15%)	116 (17%)	615 (13%)
Female	796 (53%)	429 (51%)	786 (51%)	344 (49%)	2355 (52%)
Hispanic or Latino	538 (36%)	363 (43%)	538 (35%)	197 (28%)	1636 (36%)
Black/African American	81 (5%)	42 (5%)	77 (5%)	37 (5%)	237 (5%)
BMI ≥ 30 kg/m^2	857 (57%)	463 (55%)	883 (58%)	425 (61%)	2628 (58%)
Median days of symptom prior to randomization (IQR)	3 (2, 5)	3 (2, 4)	3 (2, 5)	3 (2, 5)	3 (2, 5)
Viral load (mean, log_{10} copies/mL)	6.25	6.30	6.23	6.20	6.24

Source: EUA 91 Amendment Table 14.1.2.1.1

D. Efficacy

1. COVID-19-related Hospitalizations and All-Cause Death

a) Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through Day 29 in the mFAS, in patients with at least one *protocol-defined* risk factor for severe COVID-19.

In the 1200 mg dose analysis, COVID-19-related hospitalization or all-cause deaths were observed in fewer patients in the REGEN-COV group compared to placebo (p=0.0024). In the 2400 mg dose analysis, COVID-19-related hospitalization or all-cause deaths were observed in fewer patients in the REGEN-COV group compared to placebo (p<0.0001) (Table 2).

The majority of events were COVID-19-related hospitalizations. There was one death through Day 29 in each of the 1200 mg and 2400 mg groups, respectively. In the placebo group, there were three deaths through Day 29 and two separate

deaths that occurred after Day 29 for a total of 5 deaths through end of study follow-up. In all groups, the cause of death was a COVID-19-related adverse event.

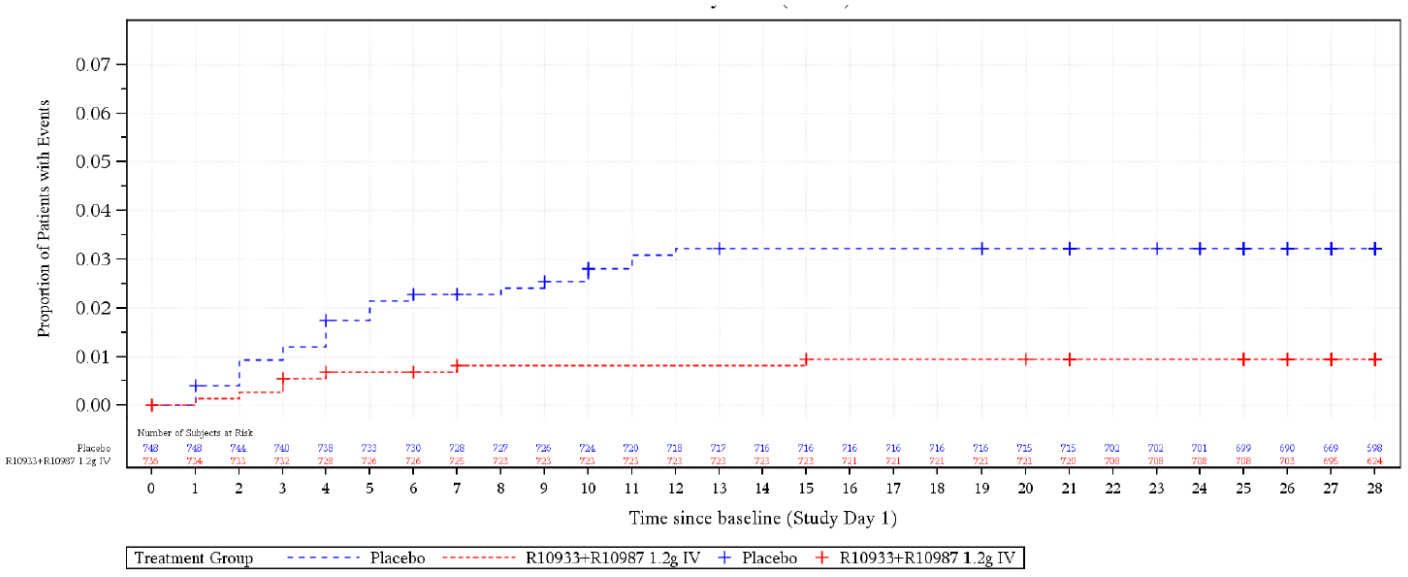
Table 2: COVID-19-Related Hospitalization and All-Cause Death Through Day 29 in Phase 3 Cohort 1 in COV-2067 (mFAS)

	1,200 mg IV[1]	Placebo[1]	2,400 mg IV[2]	Placebo[2]
	n=736	n=748	n=1,355	n=1,341
Proportion of patients with events[3] (number of patients with events[3]), n (%)	7 (1.0%)	24 (3.2%)	18 (1.3%)	62 (4.6%)
Risk reduction (95% CI) P-value[4]	70.4% (31.6%, 87.1%) p=0.0024		71.3% (51.7%, 82.9%) p<0.0001	

[1]Including patients enrolled after protocol amendment 6
[2]Including patients enrolled before and after protocol amendment 6
[3]Events referred to COVID-19-related hospitalization and all-cause mortality through Day 29
[4]The 95% CIs for relative risk reduction were based on Farrington-Manning method. P-values were based on Cochran-Mantel-Haenszel (CMH) test stratified by country.
Source: EUA 91 Amendment Tables 14.2.1.1.1M.1 and 14.2.1.1.1MP6

The Kaplan Meier curves (Figures 1 and 2) show the time to hospitalization and death in the 1200 mg vs. placebo analysis; and the 2400 mg vs. placebo analysis. In the 1200 mg dose group, most events (5 out of 7 total events) had occurred by day 7. In the 2400 mg dose group, most events (17 out of 18 total events) occurred by day 7.

Figure 1: Time to COVID-19-related hospitalizations and all-cause death for 1200 mg vs placebo (mFAS)



Source: EUA 91 Amendment Figure 14.2.1.1.1MP6a

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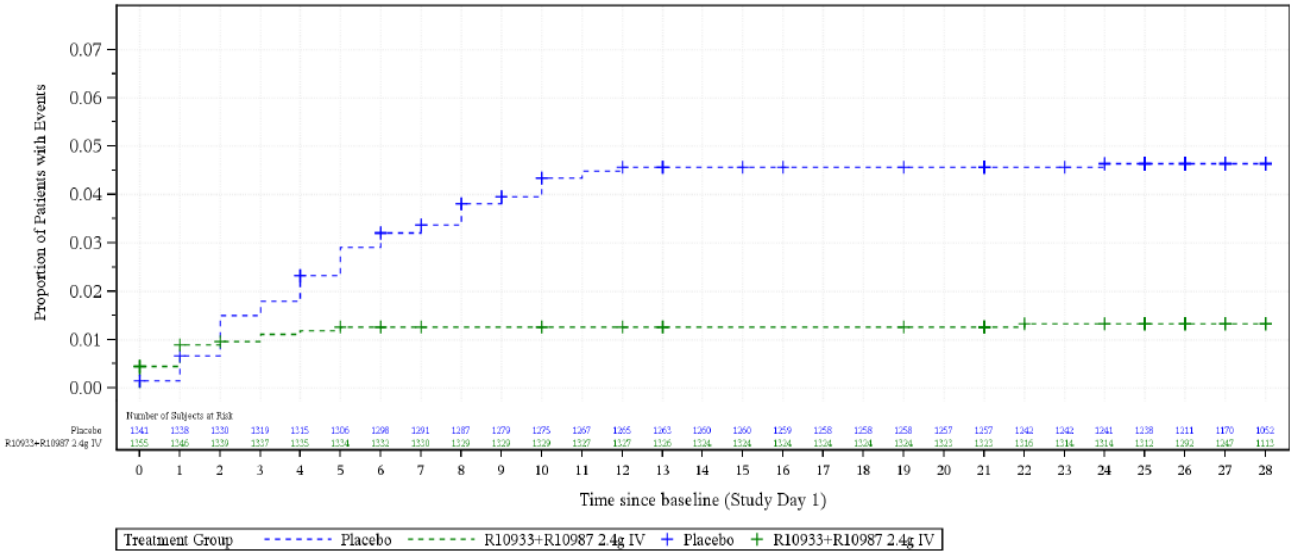
Figure 2: Time to COVID-19-related hospitalizations and all-cause death for 2400 mg vs placebo (mFAS)



Source: EUA 91 Amendment Figure 14.2.1.1.1M.1

The results from the analyses for the FAS, in patients with at least one protocol-defined risk factor were consistent with those for the mFAS, i.e., a 71.9% relative risk reduction was observed (95% confidence interval [35.5%, 87.8%]; p-value=0.0014) for the 1200 mg dose; and a 72.0% relative risk reduction was observed (95% CI [52.9%, 83.3%]; p-value of <0.0001) for the 2400 mg dose.

b) Efficacy in Original EUA High Risk Subgroup

In the subgroup of patients with high risk criteria as defined in the original EUA FS, there were fewer COVID-19-related hospitalization and all-cause deaths observed in the REGEN-COV dose group in the 2400 mg REGEN-COV vs placebo analysis (p<0.0001) and in the 1200 mg REGEN-COV vs placebo analysis (p=0.0057) (Table 3).

Table 3: Proportion of Subjects with Events of COVID-19-Related Hospitalization and All-Cause Death Through Day 29 in Subgroup with EUA High Risk Criteria (mFAS)

	1,200 mg IV[1] (N=357)	Placebo[1] (N=361)	2,400 mg IV[2] (N=692)	Placebo[2] (N=684)
Proportion of patients with events (number of patients with events), n (%)	6 (1.7%)	20 (5.5%)	16 (2.3%)	51 (7.5%)
Risk reduction (95% CI) P-value[3]	69.7% (25.3%, 87.7%) P=0.0057		69.0% (46.2%, 82.1%) P<0.0001	

[1]Including patients enrolled after protocol amendment 6
[2]Including patients enrolled before and after protocol amendment 6
[3]The 95% CIs for relative risk reduction were based on Farrington-Manning method. P-values were based on CMH test stratified by country.
Source: EUA 91 Amendment Regulatory Response submitted dated 30 March 2021 Tables 14.2.1.1.1M.3 and 14.2.1.1.4MP6 and statistical reviewer

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In considering the benefit-risk profile of REGEN-COV, it is useful to estimate the number needed to treat (NNT) to prevent one COVID-19-related hospitalization or death. The NNT to prevent one COVID-19 related hospitalized or death was 19 (95% CI based on Miettinen-Nurminen [MN] method [13, 34]), and 26 (95% CI based on MN method [14, 82]) for the 2400 mg and 1200 mg doses, respectively. For the 1200 mg dose, the 95% CI is relatively wide with the number needed to treat between 14 and 82 high risk patients to prevent one additional event of hospitalization or death. This uncertainty may stem from the relatively small sample size and number of events.

c) Subgroup Analysis for Individual High Risk Factors

A trend favoring REGEN-COV compared to placebo was also observed in the subgroups defined by the individual high risk factor for severe disease (Table 4). Risk factor subgroups were not part of the prespecified hierarchical phase 3 analysis; however, it should be noted that nominally significant treatment differences, for the 1200 mg dose and the 2400 mg dose compared to placebo, were observed in some subgroups e.g., age 50 years or older, or in the subgroup of patients with BMI ≥30 kg/m^2. Regardless of the specific risk factor, there is a trend for reduction in events with the 1200 and 2400 mg doses compared to placebo. There were very few events in some other subgroups e.g., chronic liver disease, kidney disease. The Applicant did not collect data for some CDC-specified high risk factors including substance abuse disorder, dementia, stroke or cerebrovascular disease, and Down syndrome. There were no events in the REGEN-COV 1200 mg or 2400 mg dose subgroups with no risk factors (enrolled in phase 3 prior to protocol amendment 6), compared to 2 events (0.5%) in the concurrent placebo group with no risk factors.

Table 4: Subgroup Analysis for High Risk Factors (mFAS)

Population	Dose group	N	Events[1]	Proportion of subjects with event[1]	Relative risk reduction[2]
Age ≥50 years	Placebo	678	52	7.7%	72.6%, 95% CI (51.9%, 84.4%), nominal p<0.0001
	2400 mg	715	15	2.1%	
	Placebo	356	19	5.3%	63.3%, 95% CI (13.7%, 84.4%), nominal p=0.0166
	1200 mg	357	7	2.0%	
Obesity (BMI ≥30 kg/m^2)	Placebo	772	38	4.9%	66.4%, 95% CI (37.5%, 82.0%), nominal p=0.0003
	2400 mg	787	13	1.7%	
	Placebo	427	15	3.5%	86.1%, 95% CI (39.7%, 96.8%), nominal p=0.0022
	1200 mg	410	2	0.5%	
Cardiovascular disease including hypertension	Placebo	473	40	8.5%	84.1%, 95% CI (64.8%, 92.8%), nominal p<0.0001
	2400 mg	520	7	1.3%	
	Placebo	266	15	5.6%	68.6%, 95% CI (14.7%, 88.4%), nominal p=0.0211
	1200 mg	282	5	1.8%	
Chronic metabolic disease including diabetes	Placebo	210	17	8.1%	51.1%, 95% CI (-10.8%, 78.4%), nominal p=0.0842
	2400 mg	202	8	4.0%	
	Placebo	100	6	6.0%	64.5%, 95% CI (-71.4%, 92.7%), nominal p=0.2807
	1200 mg	94	2	2.1%	
Chronic liver disease	Placebo	8	1	12.5%	100% nominal p=0.3636
	2400 mg	14	0	0%	
	Placebo	4	0	0%	No events
	1200 mg	3	0	0%	
Chronic kidney disease including those on dialysis	Placebo	9	4	44.4%	76.3%, 95% CI (-6.2%, 94.7%), nominal p=0.0638
	2400 mg	19	2	10.5%	
	Placebo	4	1	25.0%	50.0%, 95% CI (-508.2%, 95.9%), nominal p=1.0000
	1200 mg	8	1	12.5%	
Chronic lung disease including asthma	Placebo	219	14	6.4%	63.8%, 95% CI (1.2%, 86.7%), nominal p=0.0580
	2400 mg	216	5	2.3%	
	Placebo	139	6	4.3%	83.3%, 95% CI (-36.6%, 98.0%), nominal p=0.1203
	1200 mg	139	1	0.7%	
Immunosuppressed	Placebo	34	2	5.9%	26.1%, 95% CI (-398.7%, 89.0%), nominal p=1.0000
	2400 mg	46	2	4.3%	
	Placebo	10	1	10.0%	100% nominal p=0.2941
	1200 mg	24	0	0%	
Higher Risk of Severe COVID-19, excluding age >50 years, but including age ≥65 years	Placebo	144	21	14.6%	71.2%, 95% CI (38.8%, 86.4%), nominal p=0.0004
	2400 mg	214	9	4.2%	
	Placebo	88	10	11.4%	71.6%, 95% CI (0.2%, 91.9%), nominal p=0.0439
	1200 mg	93	3	3.2%	
Age >55 years AND ≥1 of the following: cardiovascular disease, hypertension, COPD or chronic respiratory disease	Placebo	227	27	11.9%	81.4%, 95% CI (55.7%, 92.2%), nominal p<0.0001
	2400 mg	271	6	2.2%	
	Placebo	131	10	7.6%	48.0%, 95% CI (-47.9%, 81.7%), nominal p=0.2886
	1200 mg	126	5	4.0%	
No Risk Factors (only applicable prior to protocol amendment 6)	Placebo	126	5	4.0%	100% nominal p=0.4999
	2400 mg	369	2	0.5%	
	Placebo	344	0	0	100% nominal p=0.5011
	1200 mg	327	0	0	

[1]Events refer to COVID-19-related hospitalization and all-cause mortality through Day 29
[2]P-value was based on CMH test stratified by country, or Fisher exact test if expected event frequency is ≤ 5 in any treatment group. The 95% CI for relative risk reduction was based on Farrington-Manning method.
Source: EUA 91 Amendment Regulatory Response submitted dated 30 March 2021 Table 4

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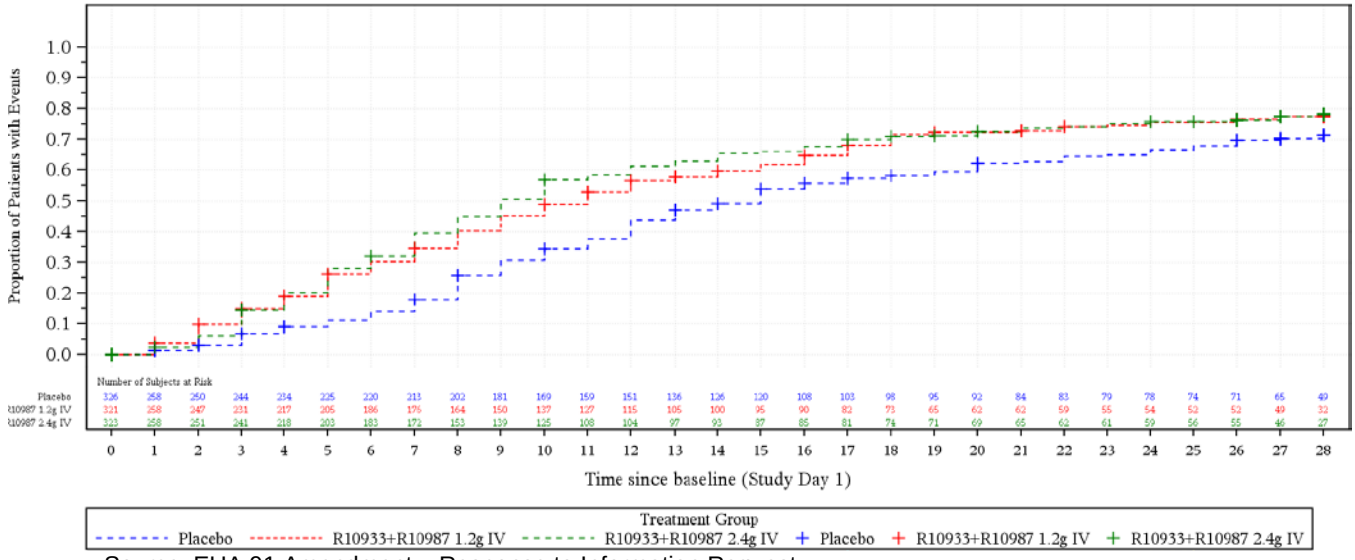
2. Effects on COVID-19 Symptom Endpoint

Trial participants used a daily questionnaire to rate their symptoms as 0 = none or absent, 1 = mild, 2 = moderate, or 3 = severe. 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.

One of the key secondary endpoints was time to COVID-19 symptom resolution. Time to COVID-19 symptom 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 2) or 'no symptom' (score of 0).

As shown in Figure 3, the median time to symptom resolution was 10 days for REGEN-COV as compared to 14 days for the placebo group; this difference was statistically significant for both dose groups (p=0.0001 for 1,200 mg vs. placebo; p<0.0001 for 2,400 mg vs. placebo).

Figure 3: Time to Symptom Resolution (mFAS)



Source: EUA 91 Amendment – Response to Information Request

3. Effects on Viral Load

Treatment with REGEN-COV 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 1,200 mg and -0.86 log_{10} 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

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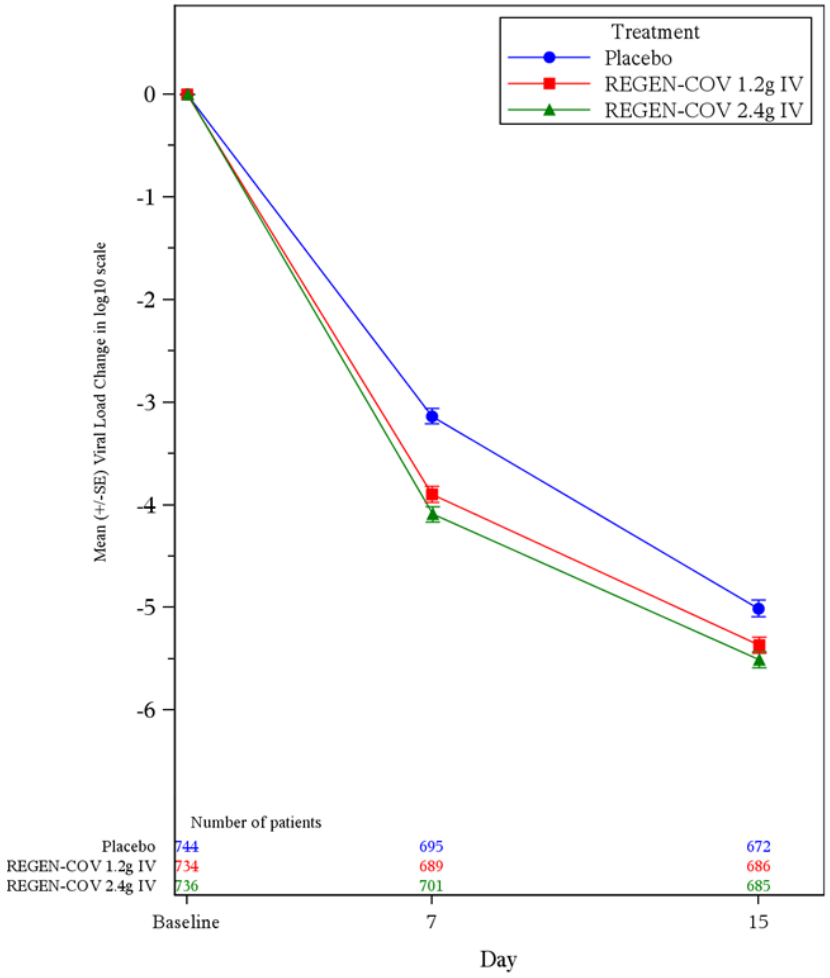
who were seronegative at baseline. Consistent effects were observed for the individual doses, indicating the absence of a dose effect (Figure 4).

Figure 4: Change from Baseline in SARS-COV-2 Viral Load (log_{10} copies/mL) to Day 15



REGEN-COV 1.2 g IV = 600 mg of casirivimab and 600 mg of imdevimab administered intravenously
REGEN-COV 2.4 g IV = 1,200 mg of casirivimab and 1,200 mg of imdevimab administered intravenously
Source: EUA 91 Amendment – Response to Information Request

4. Effects of 1200 mg Dose on SARS-CoV-2 Variants of Concern

Currently, there are no clinical data available to determine whether the proposed dose is effective against Variants of Concern (VOC). The Applicant provided an assessment based on the neutralization activity (EC_{90} value) from pseudotyped virus-like particle (VLP) assays. These EC_{90} values were used to predict *in vivo* efficacy. Our assessment is primarily focused on the E484K substitution because of its occurrence in several variants of concern. The E484K substitution is

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present in variants of B.1.351, P.1, and B.1.526 lineages and has shown reduced susceptibility to casirivimab alone in pseudotyped VLP neutralization assays. The Applicant provided a ratio of serum concentration of mAbs on Day 29 to the EC_{90} values for wild type (WT) and the variant with the E484K substitution. These data showed that at the 1200 mg dose, the serum concentration of casirivimab and imdevimab were >100-fold and >900-fold higher, respectively, than the EC_{90} value for the variant with the E484K substitution. Based on these data, the Applicant concluded that the decreased potency of casirivimab against the E484K substitution would not reduce the efficacy of the combination of casirivimab and imdevimab at the proposed dose of 1200 mg IV based on the neutralization activity of the combination in the pseudotyped VLP assay. However, this approach did not take target tissue distribution into consideration.

To evaluate whether the concentration of casirivimab and imdevimab would be adequate to provide coverage of current variants of concern/variants of interest, the review team used an inhibitory-quotient (IQ) approach. The IQ was calculated as the ratio of predicted lung concentrations on Day 29 or Day 7 relative to the EC_{90} value. Day 7 was evaluated as most clinical events related to COVID-19 disease progression occurred within seven days after drug or placebo treatment. Day 29 was selected as the proportion of patients with COVID-19-related hospitalization or all-cause death through Day 29 was the phase 3 primary efficacy endpoint. Concentrations in the lung tissue were estimated using a 1% partition ratio from serum to lung tissue. The 1% percent value was chosen as a conservative estimate because it is the lower end of the reported range of lung to plasma partition ratio values for mAbs (up to 25%, Shah DK, Betts AM, 2013; Wollacott AM et al, 2016; Eigenmann MJ et al, 2017; Magyarics Z et al 2019). A conservative approach was used because the values come from different parts of the respiratory tract and it is unclear which part of the respiratory tract is the relevant site of action. In addition, multiple different methodologies were used in the publications (PBPK, nasal swab or bronchoalveolar lavage), which could affect the accuracy of the prediction.

The predicted lung concentrations on Day 29 and Day 7 which were used to calculate the IQs are shown in Table 5.

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Table 5: Predicted Lung Concentrations of Casirivimab and Imdevimab, EC_{90} Values, and IQ Values for WT and E484K Substitution

	Casirivimab 600 mg	Imdevimab 600 mg
C29-serum (mcg/mL)	41.5	34.6
C29-lung (mcg/mL)[a]	0.415	0.346
C7-serum (mcg/mL)[b]	68.2	63.5
C7-lung (mcg/mL)[a]	0.682	0.635
In vitro EC90 WT (mcg/mL)	0.034	0.031
In vitro EC90 E484K (mcg/mL)[c]	0.609	0.041
Fold-Shift in EC90 for E484K	18.0	1.3
IQ (C29-serum/EC90-WT)	1226.4	1106.2
IQ (C29-serum/EC90-E484K)	68.2	854.3
IQ (C7-serum/EC90-WT)	2015.5	2030.2
IQ (C7-serum/EC90-E484K)	112.1	1567.8
IQ values with predicted lung concentrations		
IQ (C29-lung/EC90-WT)	12.3	11.1
IQ (C29-lung/EC90-E484K)	0.682	8.5
IQ (C7-lung/EC90-WT)	20.2	20.3
IQ (C7-lung/EC90-E484K)	1.1	15.7

C_{29}: concentration on Day 29, C_7: concentration on Day 7

[a] A 1% lung to plasma ratio was chosen to provide a conservative assessment

[b] Simulated Day 7 concentration in serum following single IV dose of casirivimab and imdevimab (1200 mg)

[c] Mean EC_{90} value from three experiments using pseudotyped VLP assays for WT and variants; authentic virus data were not available for variants at time of review

The analysis indicates that imdevimab is expected to retain maximal antiviral activity for at least 29 days after administration. Because imdevimab does not lose potency in a pseudotyped VLP assay against the E484K substitution, it is likely that imdevimab will provide sufficient coverage in the clinical setting against variants of concern or variants of interest. The IQ of casirivimab is 1.1 on Day 7, suggesting that casirivimab may retain activity against E484K for at least 7 days after administration. While the IQ of casirivimab is 0.68 on Day 28 after administration, this is not likely to be clinically relevant, based on the time course of the disease. Also, because a conservative approach was used, a low IQ value (e.g., less than one) does not necessarily indicate that there will be a loss of activity.

REGEN-COV had the highest fold change in EC_{90} value against the E484K substitution in a pseudotyped VLP assay compared with spike protein and/or substitutions from other variants of concern/variants of interest tested in this assay, including the E484Q substitution found in the B.1.617 lineage. Hence, based on the above analyses for the individual mAbs, it is likely that 1200 mg REGEN-COV will provide sufficient coverage for other currently circulating variants of concern/variants of interest, including those from B.1.1.7,

B.1.427/B.1.429, B.1.351, P.1. and B.1.617 lineages. In conclusion, the 1200 mg dose is anticipated to maintain activity against currently circulating variants of concern/variants of interest, based on information available at the time of review.

Efficacy Conclusion

A clinically and statistically significant reduction in COVID-19-related hospitalization and all-cause death through study day 29 was observed with 1200 mg REGEN-COV compared to the concurrent placebo group in symptomatic patients with at least one CDC high risk factor for severe COVID-19. The magnitude of clinical response, approximately 70% reduction in hospitalization and death, was similar in the 1200 mg vs placebo analysis and the 2400 mg vs placebo analysis. Similar responses were observed with the 1200 mg dose compared to the 2400 mg dose for secondary endpoints of median time to resolution of COVID-19 symptoms, and mean change in viral load from baseline to day 7.

Given the timing of conduct of COV-2067, we anticipate that a small proportion of patients in this trial may have been infected with currently circulating SARS-CoV-2 variants of concern or variants of interest, including B.1.526 (New York origin). However, genotypic data from COV-2067 and another outpatient treatment trial COV-20145 are not available at the present time and are anticipated in July 2021.

Neutralization results from authentic virus experiments with variant viruses are also not available at the present time. For neutralization data with authentic variant virus isolates, the Applicant is relying on two independent collaborations; one with (b) (4) at Columbia University, and the other with (b) (4) at the University of Maryland, (b) (4). The currently ongoing authentic virus studies are with B.1.1.7, B.1.351, P.1 and B.1.617.1 isolates. Given some inconsistencies with the authentic virus data, the Applicant is currently awaiting the conduct and results from planned repeat studies.

Based on currently available pseudotyped virus-like particle neutralization data and estimated concentrations of casirivimab and imdevimab, the 1200 mg dose of REGEN-COV is expected to retain clinical efficacy against currently circulating variants of concern/variants of interest.

E. Clinical Safety

Overall, approximately 9000 clinical trial participants, both non-hospitalized and hospitalized, have received REGEN-COV intravenously as single doses ranging from 1200 mg (600 mg of each mAb) to 8000 mg (4000 mg of each mAb). The phase 3 safety analysis is for the FAS in Cohort 1. A total 5531 patients were

dosed in phase 3 as follows: 1200 mg REGEN-COV (n=827), 2400 mg REGEN-COV (n=1849), 8000 mg REGEN-COV (n=1012), or placebo (n=1843).

Overall, the frequency of treatment emergent adverse events (TEAE) was similar in the REGEN-COV dose groups (7-8%) and lower than in the placebo group (10%) (Table 6). A total of 7 deaths were reported including 1 death each in the 1200 mg dose group (<1%) and the 2400 mg dose group (<1%), no deaths in the 8000 mg dose group, and 5 deaths in the placebo arm (<1%). In each case, the adverse event (AE) leading to death was assessed as unrelated to study treatment by the investigator. The cause of death was a COVID-19 event in each case.

Serious adverse events (SAEs) were reported in fewer patients in the REGEN-COV dose groups (1-2%) compared to placebo (4%). All SAEs were assessed as related to COVID-19 or to clinical complications of COVID-19. The SAEs that were observed in more than 2 subjects in the REGEN-COV dose groups were COVID-19, COVID-19 pneumonia, pneumonia, and acute respiratory failure. Grade 3 or 4 treatment-emergent AEs were also observed in fewer patients in the REGEN-COV dose groups (1-2%) compared to placebo (3%).

Table 6: Safety overview in Phase 3 in COV-2067 (Cohort 1, FAS)

	1200 mg IV REGEN-COV (N=827) n/%	**2400 mg IV REGEN-COV (N=1849) n/%**	**8000 mg IV REGEN-COV (N=1012) n/%**	**Placebo (N=1843) n/%**
Patients with at least 1 TEAE	59 (7)	142 (8)	85 (8)	189 (10)
Deaths	1 (<1)	1 (<1)	0	5 (<1)
Patients with ≥1 SAE	9 (1)	24 (2)	17 (2)	74 (4)
Patients with Grade 3 or 4 TEAEs	11 (1)	18 (1)	15 (2)	62 (3)
Patients with TEAE leading to study withdrawal	0	1 (<1)	2 (<1)	1 (<1)
Patients with ≥grade 2 infusion related reactions through Day 4	2 (<1)	1 (<1)	3 (<1)	0
Patient with ≥ grade 2 hypersensitivity reaction through Day 29	0	1 (<1)	0	1 (<1)

TEAE=treatment emergent adverse event; SAE=serious adverse event; AESI=adverse event of special interest
Source: EUA 91 Amendment Table 14.3.2.1SA

Hypersensitivity including Anaphylaxis and Infusion-related Reactions

In Phase 3, infusion-related reactions of grade 2 or higher severity, were observed in few subjects in the 1200 mg (n=2), 2400 mg (n=1), and 8000 mg (n=3) dose groups compared to no events in the placebo group. All events were mild or moderate in severity. The events were nausea with dizziness and headache (n=1; 1200 mg REGEN-COV), urticaria (n=1; 2400 mg), shortness of

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breath, chest tightness (n=1; 2400 mg), nausea and vomiting (n=1; 8000 mg), hyperresponsive to stimuli and diaphoresis (n=1; 8000 mg), rash (n=1; 8000 mg), and infusion-related reaction (n=1; 8000 mg).

In three patients, treatment was interrupted secondary to infusion-related reactions. One patient receiving 2400 mg REGEN-COV withdrew treatment after developing shortness of breath, flushing and chest tightness; the events were grade 2 in severity. One patient receiving 8000 mg REGEN-COV discontinued treatment secondary to a grade 2 infusion-related reaction; the event resolved after infusion interruption. A separate patient receiving 8000 mg REGEN-COV withdrew treatment after developing a grade 2 rash. In each case, the events resolved after treatment discontinuation.

Additionally, in the pooled phase 1, 2, and 3 analysis in this trial, grade 2 or higher infusion-related reactions were observed in 0.2% (10/4206) of patients treated with REGEN-COV compared to <0.1% (1/2105) in the placebo group.

One case of anaphylactic reaction was reported in a patient who received 8000 mg REGEN-COV (4000 mg of casirivimab and 4000 mg of imdevimab intravenously) in the phase 1 and 2 portion of a clinical trial in hospitalized patients, COV-2066. This case was identified at the time of issuance of the original EUA and is described in the HCP FS. The Division recently received a MedWatch report for a separate case of anaphylaxis in a patient receiving the 1200 mg dose (600 mg of casirivimab and 600 mg of imdevimab) in COV-2067; this event was identified after the data cut-off for phase 3 analysis and therefore the event is not included in the phase 3 analysis safety summary submitted to support the EUA amendment. In both cases, patients recovered after receiving appropriate treatment. The safety section 6.1 of the HCP FS was updated for the recently identified case in COV-2067.

Safety Conclusion

In summary, grade 2 infusion-related reactions were observed in 0.2% of trial participants treated with REGEN-COV at any dose in COV-2067. Two cases of anaphylaxis or anaphylactic reaction were observed in the overall clinical program. This includes one case from trial COV-2066, in hospitalized patients, which was identified at the time of issuance of the original EUA; and a separate case which occurred in the phase 3 portion of COV-2067, the outpatient treatment trial, after the data cut-off timepoint for the phase 3 analysis. The safety profile in phase 3 is similar to the safety profile observed in phases 1 and 2 of COV-2067.

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F. Overall Assessment for 1200 mg Dose for Treatment

Based on the phase 3 results, the known and potential benefits outweigh the known and potential risks for the proposed 1200 mg REGEN-COV (600 mg of casirivimab and 600 mg of imdevimab) for a clinically important endpoint of reduction of COVID-19-related hospitalizations and all-cause death through Day 29. These data support authorization of the lower 1200 mg dose for the following reasons:

- A clinically and statistically significant reduction in COVID-19-related hospitalization and all-cause death through study day 29 was observed with 1200 mg REGEN-COV compared to the concurrent placebo group in symptomatic patients with at least one CDC high risk factor for severe COVID-19. The magnitude of clinical response, approximately 70% reduction in hospitalization and death, was similar in the 1200 mg vs placebo analysis and the 2400 mg vs placebo analysis.
- Similar responses were observed with the 1200 mg dose compared to the 2400 mg dose in subgroup analyses (for example, for subgroup with EUA-defined high risk criteria, or by individual high risk subgroups) and for the secondary endpoints of median time to resolution of COVID-19 symptoms, and mean change in viral load from baseline to day 7.
- The safety profile was generally similar in the two dose groups.
- Given the timing of phase 3, we anticipate that a small proportion of phase 3 patients may have been infected with currently circulating SARS-CoV-2 variants of concern or variants of interest, including B.1.526 (New York origin). Genotypic data from phase 3 studies and nonclinical neutralization results from authentic virus experiments with variant viruses are not available at the present time. Based on available pseudotyped virus-like particle neutralization data and estimated concentrations of casirivimab and imdevimab, the 1200 mg dose of REGEN-COV is expected to retain activity against currently circulating variants of concern and variants of interest. As novel variants of concern/variants of interest are identified, the Applicant will assess the neutralizing activity against variants to ensure susceptibility to casirivimab and imdevimab and to the combination.

III. Data Supporting the Alternative Subcutaneous Administration

Intravenous administration is the currently authorized route of administration. The Applicant proposed subcutaneous administration as an additional dosing route.

We considered the Applicant's proposal, the available supporting clinical data for subcutaneous dosing, and the need for subcutaneous dosing. Specifically, we

considered the clinical need for an alternative to IV dosing in specific situations where IV access is not feasible and would result in delay in treatment initiation in a high risk patient, as well as clinical pharmacology considerations with subcutaneous dosing, as outlined below. As the subcutaneous route of administration slows the rate the monoclonal antibodies appear in systemic circulation, the clinical pharmacology team considered PK and PD (viral load reduction) data following the administration of 1200 mg IV and 1200 mg subcutaneous doses of REGEN-COV to support the1200 mg subcutaneous dose.

There is no ongoing or completed clinical trial demonstrating the clinical efficacy of REGEN-COV when administered as a 1200 mg subcutaneous dose for treatment of COVID-19 patients. Subcutaneous dosing is typically associated with a slower absorption as compared to IV dosing. This would result in a delay in achieving critical concentrations at the site of pharmacological action as compared to IV dosing. While the clinical relevance of such a delay for monoclonal antibodies targeting SARS-CoV-2 is unknown at this time, a simple exposure matching approach using AUC or concentrations at later time points (e.g., Day 7, 14, or 28 concentrations) is not sufficient alone to bridge the efficacy from IV dosing to subcutaneous dosing.

To support the authorization of 1200 mg subcutaneous dosing, the Applicant proposed a totality of evidence approach using efficacy, safety, and PK data collected across all clinical trials. The review team has concluded that PK and PD (viral load reduction) data can support the use of a 1200 mg subcutaneous dose for treatment of COVID-19 when IV dosing is not feasible and would result in a delay in treatment.

A. Comparable viral load reduction following the administration of 1200 mg IV and 1200 mg subcutaneous of REGEN-COV

Although use of viral load as a surrogate endpoint to predict clinical outcomes has not been established at this time, it is reasonable to use viral load data as part of the totality of evidence to support a change in the route of administration when the clinical benefit of REGEN-COV has been demonstrated with IV dosing.

In Study COV-20145, a dose-ranging study in outpatients, the viral load reduction in the nasopharynx (NP) following a 1200 mg subcutaneous dose was superior to placebo and similar to a 1200 mg IV dose (See Figure 5). There was no difference in viral load reduction between a 1200 mg subcutaneous dose and a 1200 mg IV dose based on a pairwise comparison using time-weighted average daily change from baseline in viral load from Day 1 through Day 7. There was also no apparent difference between subcutaneous and IV dosing at earlier timepoints, Day 3, or Day 5. Although

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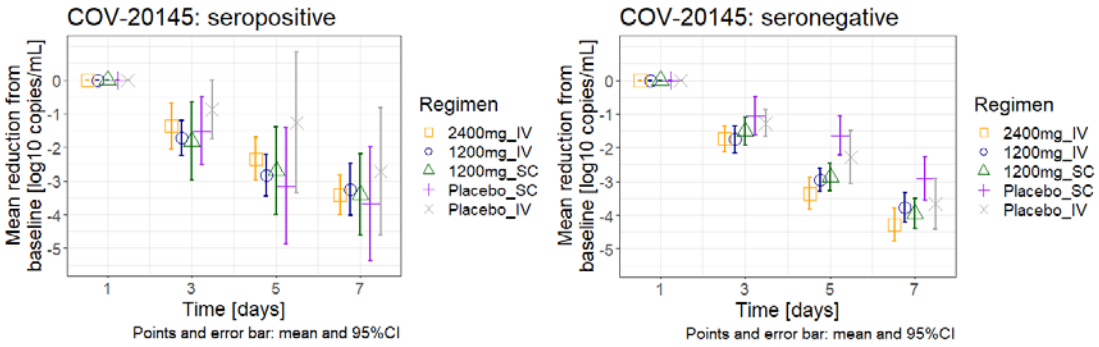
the most critical virologic endpoints to demonstrate comparability between IV and subcutaneous dosing are unknown at this time, viral load reductions at all available time points on or before Day 7 indicate a comparable viral load reduction between IV and subcutaneous dosing. In addition, there was no clear dose-response relationship for the viral load reductions at Day 3, 5, and 7 with all doses evaluated in the study (300 mg IV, 600 mg IV, 1200 mg IV, 2400 mg IV, 600 mg subcutaneous, and 1200 mg subcutaneous), indicating that antiviral activity with 1200 mg subcutaneous is likely on the plateau of the dose/exposure-response relationship.

Figure 5: Comparison of viral load reduction between IV and SC including all subjects (both seropositive and seronegative)



B. Assessment of implications of a delay in exposure (a slower absorption rate with subcutaneous dosing)

A summary of PK parameters after administration of a single 1200 mg IV dose and a single 1200 mg subcutaneous dose is provided in Tables 7 and 8.

Table 7: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 1200 mg IV REGEN-COV Dose in Phase 3 of Study COV-2067

PK Parameter[1]	Casirivimab	Imdevimab
C_{eoi} (mg/L)[2]	192 (80.9)	198 (84.8)
C_{28} (mg/L)[3]	46.2 (22.3)	38.5 (19.7)

[1] Mean (SD)
[2] Concentration at end of 1-hour infusion; eoi = end of infusion
[3] Observed concentration 28 days after dosing, i.e., on day 29, as defined in the protocol

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Table 8: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 1200 mg subcutaneous REGEN-COV Dose

PK Parameter[1]	Casirivimab	Imdevimab
C_{max} (mg/L)	55.6 (22.2)	52.7 (22.5)
t_{max} (day)[2]	8.00 (4.00, 87.0)	7.00 (4.00, 15.0)
AUC_{0-28} (mg●day/L)	1060 (363)	950 (362)
AUC_{inf} (mg●day/L)[3]	2580 (1349)	1990 (1141)
C_{28} (mg/L)[4]	30.7 (11.9)	24.8 (9.58)
Half-life (day)	31.8 (8.35)	26.9 (6.80)

[1] Mean (SD)
[2] Median (range)
[3] Value reported for subjects with %AUC_{inf} extrapolated <20%
[4] Observed concentration 28 days after dosing, i.e., on day 29

Estimated Time to Achieve Target Concentration

As there is a concern of delayed onset of pharmacological action with subcutaneous dosing due to a slower absorption compared to IV dosing, the time to reach the target concentrations of casirivimab and imdevimab was estimated. Assuming a lung-to-serum ratio of 1% (for the basis and limitation of this assumption see Section II.D.4, Effects of 1200 mg Dose on SARS-CoV-2 Variants of Concern), target serum concentrations of 3.4 mg/L for casirivimab and 3.1 mg/L for imdevimab were derived using the EC_{90} of the WT virus strain. Casirivimab and imdevimab concentrations (mean, SD) were 9.8 ± 31.4 mg/L (n=59) and 8.0 ± 29.8 mg/L (n=80), respectively, 0-2 hours after a 1200 mg subcutaneous dose (Study COV-20145). Casirivimab and imdevimab concentrations were 22.7 ± 11.5 (n=13) and 23.0 ± 12.9 (n=13), respectively, 16 to 24 hours after a 1200 mg subcutaneous dose (Figure 6). Casirivimab and imdevimab concentrations in lung tissue are expected to reach concentrations needed for antiviral activity within 24 hours of subcutaneous administration.

We acknowledge that there are limitations with this approach. First of all, the approach uses the assumption that there is a rapid equilibrium between plasma and lung tissue concentrations. Second, there are limited PK data prior to 16 hours post dose and it is not feasible to precisely determine the time to reach the target concentrations. Despite these limitations, it is reasonable to conclude that the target concentrations are likely to be reached within a day of administration, when coupled with viral load reduction data and conservative assumptions on the lung to plasma partition ratio.

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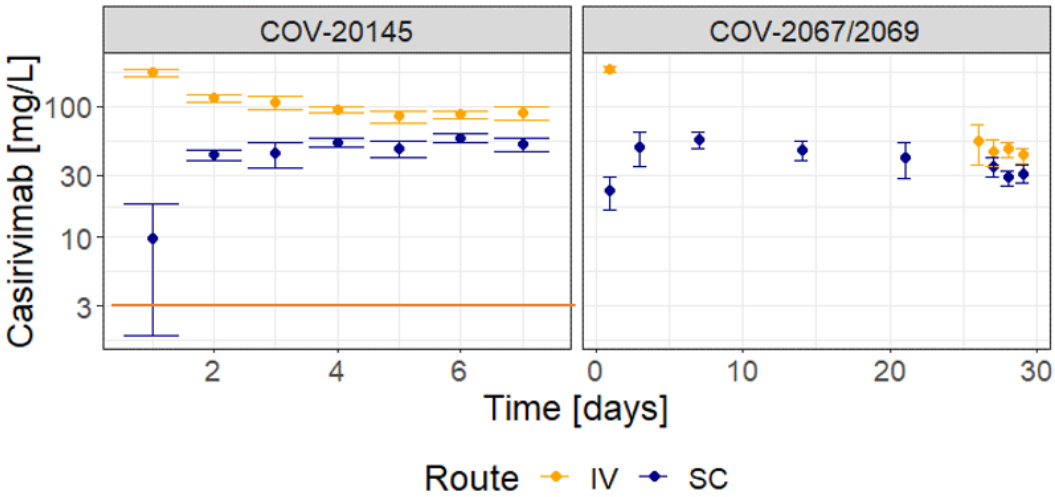
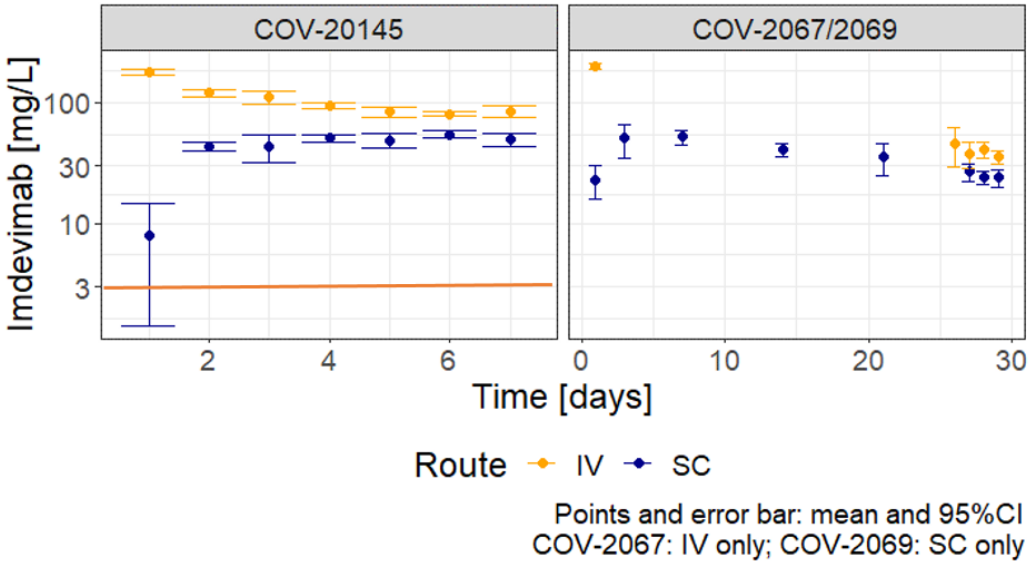
Figure 6: Concentrations (log scale) of Casirivimab and Imdevimab in Serum After Single 1200 mg Subcutaneous and 1200 mg IV REGEN-COV Doses in Studies COV-2067/COV-2069 and COV-20145 (Review Team's Analysis)





COV-20145: data represented for Day 1 were collected 0-2 hours post subcutaneous dose and 0.5-2.5 hours post IV dose
COV-2067: data represented for Day 1 were collected 0.3-3.3 hours post IV dose
COV-2069: data represented for Day 1 were collected 16-24 hours post subcutaneous dose

Safety Assessment

The safety of 600 mg of casirivimab and 600 mg of imdevimab administered subcutaneously is based on analysis from R10933-10987-HV-2093 (NCT

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04519437), a randomized double-blind, placebo-controlled trial evaluating the safety and pharmacokinetic profile in healthy volunteer adult subjects.

The safety profile of single subcutaneous dose and multiple subcutaneous doses administered at four week intervals is being evaluated in this ongoing trial. Adult subjects were randomized 3:1 to REGEN-COV (n=729) or placebo (n=240). The mean age was 47 years; and 13% were 65 years and older. Approximately 55% of the study population were female; and approximately 10% and 23% were African American or Hispanic. The mean BMI was 29 kg/m^2.

At least one TEAE was observed in 52% and 46% of subjects in the REGEN-COV and placebo arms, respectively. The most common TEAE was injection site reactions (ISRs); which were observed in 35% and 16% of subjects in the casirivimab and imdevimab and placebo arms, respectively, with multiple dosing. The ISR adverse events observed in at least 2% of subjects in the any group were erythema (27% REGEN-COV vs. 6% placebo), pruritus (13% REGEN-COV vs. 0.5% placebo), nodule (13% REGEN-COV vs. 1% placebo), edema (10% REGEN-COV vs. 1% placebo), ecchymosis (6% REGEN-COV vs. 6% placebo), pain (5% REGEN-COV vs. 2% placebo), and tenderness (3% REGEN-COV vs. 1% placebo).

The incidence of ISRs increased with repeat dosing, specifically with the fifth and sixth dose. The reason for the observed higher rate of ISRs with dose #5 or #6 is not completely understood at this time. Pertinent to this review for single dose administration for treatment, i.e. dose #1, ISRs were observed in 12% and 4% of subjects in the casirivimab and imdevimab and placebo arms, respectively, with the first dose. All ISRs were mild to moderate in severity with no grade 3 or 4 events. The median time to resolution was similar in the REGEN-COV and placebo arms. The median time to resolution was 2.0 days (1-43 days) in the REGEN-COV arm, and 2.5 days (1-16 days) in placebo arm.

Table 9: Proportion of Subjects with Injection Site Reactions in COV-2093

	REGEN-COV 600 mg casirivimab and 600 mg imdevimab subcutaneous (n=729)	**Placebo subcutaneous (n=240)**
Dose #1	89/720 (12%)	10/240 (4%)
Dose #2	93/708 (13%)	7/236 (3%)
Dose #3	93/692 (13%)	7/226 (3%)
Dose #4	83/669 (12%)	5/218 (2%)
Dose #5	113/627 (18%)	9/198 (5%)
Dose #6	107/457 (23%)	8/144 (6%)

ISR, injection site reaction; N, number; %; percentage

The remaining safety findings with subcutaneous administration in the casirivimab and imdevimab arm were similar to the safety findings observed with IV administration. Apart from ISRs, commonly occurring TEAEs observed in at

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least 2% of subjects in any group were headache (8% in each arm), fatigue (3% in each arm), nausea (3% in each arm), and oropharyngeal pain (3% in each arm). The majority of the events resolved without medical management; with few subjects in the casirivimab and imdevimab arm requiring analgesics and anti-allergic medications or antihistamines for these events.

There was one death in the trial; this was a 72-year-old subject in the REGEN-COV arm who died due to complications of diabetes and the event occurred on study day 171 during the follow-up period. The event was assessed by the investigator as not related to the study treatment. Serious adverse events were reported in 4 subjects including 3 subjects in the REGEN-COV arm and 1 subject in the placebo arm. All four SAEs were assessed to be unrelated to study treatment. The SAEs were enteritis (n=1) in the placebo arm; and the following SAEs in the REGEN-COV arm: angina pectoris (n=1), post laminectomy syndrome (n=1), post-traumatic stress disorder (n=1). Eight (1%) and 11 (5%) subjects in the REGEN-COV and placebo arm, respectively, discontinued due to an AE.

The most common reason for discontinuation was COVID-19 infection. Symptomatic COVID-19 infections were observed in 3 (0.4%) and 12 (5%) of subjects in the REGEN-COV and placebo arms, respectively, in this phase 1 healthy volunteer trial.

Conclusion

Based on the available clinical data including PK and safety data for IV and subcutaneous administration of single dose of 600 mg of casirivimab and 600 mg of imdevimab, it is reasonable to conclude that subutaneous administration is acceptable in those situations where IV administration is not feasible and may result in treatment delay, noting that IV administration is the recommended and preferred dosing route. Viral load reductions, while limited in scope given lack of viral load collection in the first 48 hours after dosing and other limitations discussed previously, indicate a similar magnitude of viral load reduction with both 1200 mg IV or subcutaneous dosing. The primary concern is the limited data for the clinically meaningful endpoints of COVID-19 hospitalization and all-cause death with subcutaneous dosing from a dedicated efficacy trial; however, we note that the Applicant is not proposing subcutaneous dosing in lieu of the currently authorized IV dosing. The Applicant's proposal for subcutaneous dosing as an alternative in select situations when IV infusion is not feasible and would lead to delay in treatment, is adequately supported by PK/PD data as well as available clinical safety data with subcutaneous administration.

In addition to the safety concerns identified with IV dosing, injection site reactions were identified as concerns specific to subcutaneous administration. Local erythema was the most commonly occuring injection site reaction; all injection site reactions were mild to moderate in severity. In situations where the

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healthcare provider determines that IV administration is not possible and the treatment dose is administered subcutaneously, the same post-dose observation period of at least one hour is recommended. To ensure that the IV route is the preferred and primary administration route, bolded statements in the Box in the HCP Fact Sheet state that IV infusion is strongly recommended and subcutaneous injection is an alternative route when IV infusion is not feasible and would lead to delay in treatment. The justification for subcutaneous dosing is provided in the HCP FS.

IV. Authorization of Co-formulation Presentation

The Applicant proposed the introduction of co-formulation vials containing casirivimab and imdevimab. Each vial provides 600 mg of casirivimab and 600 mg of imdevimab for the treatment of adult and pediatric patients (12 years of age older weighing at least 40 kg). Product quality, manufacturing, and control information as well as the submitted labeling for the co-formulation carton and container support the addition of the co-formulated drug product presentation to the EUA. The Office of Pharmaceutical Quality (OPQ), CDER, recommends authorization of this change request to EUA 91 to allow for emergency use of a co-formulated drug product (DP) presentation that contains casirivimab and imdevimab in the same vial. For details, please refer to the OPQ review dated 05/04/2021.

V. Revisions related to Hypersensivity and Infusion-Related Reactions

Based on safety reports with REGEN-COV use under EUA, which describe events of vasovagal episodes (e.g., syncope and pre-syncope) occurring as part of infusion-related reactions in the 24 hour period after infusion completion, as well as hypersensitivity reactions occurring more than 24 hours after dosing, the Division recommends revising the HCP Fact Sheet to communicate these safety concerns.

VI. Revision of Indications of Authorized Use

As the phase 3 primary endpoint is a composite endpoint of COVID-19 hospitalizations and all-cause deaths, we determined that it is appropriate to include death in the Indications statement to further qualify the entity ‘severe COVID-19’.

VII. Regulatory Conclusion

Based on the totality of the scientific evidence available, including phase 3 results from COV-2067 as well as nonclinical activity data assessing SARS-CoV-2 variants of concern and interest, the Division has concluded that it is reasonable to believe that REGEN-COV may be effective for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and when used under the conditions described in this authorization and the authorized labeling, the known and potential benefits of REGEN-COV outweigh the known and potential risks of the product.

VIII. Summary of Revisions to the EUA Letter of Authorization

This section provides a brief summary of changes to the Letter of Authorization (LOA) for EUA 091. The Agency will re-issue the LOA for EUA 091 in its entirety authorizing a change in dosing of REGEN-COV from 2400 mg (1200 mg casirivimab and 1200 mg imdevimab) to 1200 mg (600 mg casirivimab and 600 mg imdevimab) and the addition of a new presentation consisting of a single vial containing casirivimab and imdevimab co-formulated in a 1:1 ratio for either intravenous infusion or subcutaneous injection.

New conditions will also be incorporated on the provision of samples of the authorized REGEN-COV to the U.S. Department of Health and Human Services, upon request, and the submission of certain genomic sequencing and virology information to the FDA by a specified date. The Agency has determined that these new conditions are appropriate to protect the public health or safety and will facilitate the Agency's understanding of any particular SARS-CoV-2 viral variant's susceptibility to REGEN-COV. Revisions to existing conditions on advertising and promotion and other editorial changes have also been incorporated.

IX. Summary of Revisions to EUA Health Care Provider Fact Sheet

Key revisions are shown below with additions in underlined text, and deletions in strikethrough text.

- **Revised the Indications for Authorized Use statement for the co-formulation and to further include death outcomes**, as shown below:

  AUTHORIZED USE

  The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved

product, REGEN-COV (casirivimab and~~with~~ imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together~~)~~, for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressi~~ng~~on to severe COVID-19 ~~and/or~~ including hospitalization or death.

- **Revised the authorized dosage to 600 mg of casirivimab and 600 mg of imdevimab in the Box and Section 2.2 Dosage and Administration**. Please refer to the revised HCP FS for all changes related to the revised authorized treatment dose.

- **Revised the Box, Section 2.2**, **Section 2.4 Dosage and Administration with subcutaneous dosing as an alternative route of administration, as follows:**

  Intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.

  Administration for Subcutaneous Injection

  - For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes and prepare for subcutaneous injections.
  - Administer the subcutaneous injections consecutively, each at a different injection site, into the thigh, back of the upper arm, or abdomen, except for 2 inches (5 cm) around the navel. The waistline should be avoided.
  - When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or back of the upper arms to space apart each 2.5 mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred.

  Please refer to the revised HCP FS for other changes related to subcutaneous route of administration.

- **Revised the Box, Sections 2.2 and 2.4 for the Co-formulation**

  2.4 Dose Preparation and Administration

  There are TWO different formulations of REGEN-COV:

- Casirivimab and imdevimab co-formulated solution is available as two antibodies in a 1:1 ratio in a vial.
- Casirivimab and imdevimab available as individual antibody solutions in separate vials:
    - supplied in individual vials, and supplied in a
    - dose pack. The dose pack contains individual vials of casirivimab and imdevimab, configurations that may vary in vial size, strength and appearance and are available in dose pack configurations that include 2, 5, and 8 cartons *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)].*

Please refer to the revised HCP FS for all changes related to the co-formulation presentation.

- **Revised Section 5.1 Hypersensitivity and Infusion-related Reaction**

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions
Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV (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 therapy.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of REGEN-COV. These reactions may be severe or life-threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrythmia (e.g., atrial fibrillation, tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of REGEN-COV under Emergency Use Authorization.

- **Revised Sections 6.1 and 18.1 with phase 3 results from COV-2067 and revised Section 6.1 with safety with subcutaneous dosing.** Please refer to the revised HCP FS for all related changes.

- **Revised Sections 14.2 and 14.3 with PK parameters and PD data supporting subcutaneous dosing.** Please refer to the revised HCP FS for all related changes.

- **Revised Section 15 with pseudotyped VLP data for additional spike protein substitutions/variants.** The Antiviral Resistance section was updated, as follows:

  - Fold-change data for substitutions assessed in pseudotyped VLP assays updated, including data for additional substitutions tested
  - Table 6 and associated text updated to include pseudotyped VLP data for B.1.617 lineages and associated spike protein substitutions
  - Minor editorial changes

X. Revisions to the Fact Sheet for Patients, Parents and Caregivers

HOW WILL I RECEIVE REGEN-COV (casirivimab ~~with~~ and imdevimab)?

- REGEN-COV consists of two investigational medicines, casirivimab and imdevimab, given together as a single intravenous infusion (through a vein).
- You will receive one dose of REGEN COV by intravenous infusion. The infusion will take 20 to ~~52~~ 50 minutes or longer. Your healthcare provider will determine the duration of your infusion.
- If your healthcare provider determines that you are unable to receive REGEN-COV as an intravenous infusion which would lead to a delay in treatment, then as an alternative, REGEN-COV can be given together in the form of subcutaneous injection (medicine is injected in the tissue just under the skin). One dose will consist of 4 subcutaneous injections given in separate locations around the same time.

WHAT ARE THE IMPORTANT POSSIBLE SIDE EFFECTS OF REGEN-COV (casirivimab ~~with~~ and imdevimab)?
Possible side effects of REGEN-COV are:

- Allergic reactions. Allergic reactions can happen during and after infusion with REGEN-COV. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low or high blood pressure, rapid or slow heart rate, chest discomfort or pain, weakness, confusion, feeling tired, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, feeling faint, dizziness and sweating. These reactions may be severe or life threatening.

WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?
The United States FDA has made REGEN-COV (casirivimab ~~with~~ and imdevimab) available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

REGEN-COV has not undergone the same type of review as an FDA-approved or cleared product. In issuing an EUA under the COVID-19 public health emergency, the FDA must determine, among other things, that based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives. ~~The FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that the product meets certain criteria for safety, performance, and labeling and may be effective in treatment of patients during the COVID-19 pandemic.~~ All of these criteria must be met to allow for the medicine~~product~~ to be used in the treatment of patients during the COVID-19 pandemic.

XI. Issuance of Dear Health Care Provider Letter

A Dear Healthcare Provider Letter was issued to inform practitioners and prescribers about the following key changes: the revised treatment dose of 600 mg of casirivimab and 600 mg of imdevimab, introduction of the coformulated product in a single vial containing 600 mg of casirivimab and 600 mg of imdevimab, and the alternative subcutaneous administration route if intravenous dosing is not feasible and may result in treatment delay.

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/s/

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