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

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)[1]	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)	April 23, 2021 (eCTD#0098)
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OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
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[1] If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

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Integrated Review Completion Date	July 30, 2021
Proprietary Name	n/a
Established Name/Other names used during development	casirivimab (REGN10933) and imdevimab (REGN10987)
Dosage Forms/Strengths	

	Treatment of mild to moderate coronavirus disease 2019 (COVID-19): 600 mg casirivimab and 600 mg imdevimab administered intravenously or subcutaneously. Post-exposure prophylaxis: 600 mg casirivimab and 600 mg imdevimab administered intravenously or subcutaneously. For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1 monoclonal antibodies (mAbs)
Intended Use or Need for EUA	Treatment of mild to moderate coronavirus disease 2019 (COVID-19) in 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 progression to severe COVID-19, including hospitalization or death. Post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are: • not fully vaccinated **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) **and** o have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria

	per Centers for Disease Control and Prevention (CDC) **or** o who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).
Intended Population(s)	Adult and pediatric patients (12 years of age and older weighing at least 40 kg)
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	n/a

I. EUA Determination/Declaration

On February 4, 2020, the Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

A. Recommend EUA Issuance

On November 21, 2020, casirivimab and imdevimab, administered together, were authorized for the treatment of 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 and/or hospitalization. Additional phase 3 data submitted to the Division in March 2021 demonstrated that the clinical benefit with the currently authorized dose (600 mg of casirivimab and 600 mg of imdevimab) was similar to the clinical benefit observed with the originally authorized dose (1200 mg casirivimab and 1200 mg imdevimab) resulting in revision of the authorized dose to 600 mg of casirivimab and 600 mg of imdevimab, administered together.

At this time, following review of the Applicant's amendment to EUA 00091, the Division of Antivirals (DAV), Office of Infectious Diseases (OID), Office of New Drugs, CDER recommends revising the authorization of casirivimab and imdevimab, administered together, to include an additional authorized use for post-exposure prophylaxis of COVID-19.

The EUA will now permit the use of REGEN-COV, casirivimab and imdevimab to be administered together, for the following indications:

- The treatment of mild to moderate coronavirus disease 2019 (COVID-19) in 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 progression to severe COVID-19, including hospitalization or death.
- Post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
    - not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[3]) **and**
        - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[4] **or**
        - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

B. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.

[2] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

[3] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[4] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

- Casirivimab and imdevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2.
- Based on the totality of the scientific evidence available to FDA, including data from adequate and well-controlled clinical trials, it is reasonable to believe that casirivimab and imdevimab administered together may be effective for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, **and** are not fully vaccinated[2] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[5]), **and** have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC[3] **or** who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons); and under such conditions, the known and potential benefits outweigh the known and potential risks of the drugs.
- There is no adequate, approved, and available alternative to the emergency use of casirivimab and imdevimab for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are not fully vaccinated[2] or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[6]), and have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[7] or who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).
- At present, there are three SARS-CoV-2 vaccines authorized for emergency use to prevent COVID-19. The Pfizer-BioNTech and Moderna vaccines include nucleoside-modified messenger RNA that encodes the viral spike glycoprotein of SARS-CoV-2; both vaccines are administered as a 2-dose series. The Janssen/Johnson & Johnson vaccine is a replication-incompetent recombinant adenovirus type 26 vector expressing the SARS-CoV-2 spike protein in a stabilized confirmation and is

[5] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[6] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[7] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

administered intramuscularly as a single dose. On December 11, 2020, the FDA issued the EUA for Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. On May 10, 2021, the FDA expanded the EUA for the Pfizer-BioNTech COVID-19 Vaccine to include adolescents 12 through 15 years of age. On December 18, 2020, FDA issued an EUA for the Moderna COVID-19 Vaccine for the prevention of COVID-19 caused by SARS-CoV-2 for use in individuals 18 years of age and older. On February 27, 2021, FDA issued an EUA for the Janssen COVID-19 Vaccine for the prevention of COVID-19 caused by SARS-CoV-2 for use in individuals 18 years of age and older.

III. Proposed Use and Dosing of the Product Under the EUA

Proposed Use under EUA

The EUA will now authorize REGEN-COV (casirivimab and imdevimab) for emergency use as post-exposure prophylaxis for COVID-19, in addition to the already authorized use of REGEN-COV for treatment of mild to moderate COVID-19, as detailed below.

Treatment
The EUA authorizes the use of REGEN-COV (casirivimab and 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 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 progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use:

- REGEN-COV (casirivimab with imdevimab) is not authorized for use in patients:
    - who are hospitalized due to COVID-19, OR
    - who require oxygen therapy due to COVID-19, OR
    - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Post-exposure Prophylaxis
The EUA will now permit the use of REGEN-COV (casirivimab and imdevimab) co-formulated product and REGEN-COV (casirivimab and imdevimab) supplied as individual vials to be administered together, in adult and pediatric individuals

(12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated[8] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[9]) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)[10] **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Limitations of Authorized Use:

- Post-exposure prophylaxis with REGEN-COV (casirivimab with imdevimab) is not a substitute for vaccination against COVID-19.
- REGEN-COV (casirivimab and imdevimab) is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and adolescents (age 12-17 years) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment

[8] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

[9] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[10] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)).

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of casirivimab and imdevimab under the EUA is not limited to the conditions listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Authorized Dosage under EUA

Adults and Pediatric Patients

- Treatment Dosage: The authorized dosage for adults and pediatric patients (12 years of age and older who weigh ≥40 kg) is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset. For treatment, 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.

- Post-exposure prophylaxis dosage: The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together by subcutaneous injection or together as a single intravenous infusion as soon as possible following exposure to SARS-CoV-2. For individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of

imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure.

Pregnant or Lactating patients
No dosage adjustment is recommended. Casirivimab and imdevimab are currently being studied in pregnant women and have not yet been studied in lactating women. Casirivimab and imdevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Other specific populations (e.g., geriatric patients, patients with renal or hepatic impairment)
No dose adjustment is recommended based on renal impairment. The effect of other covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of casirivimab and imdevimab is unknown.

Rationale for dose
The post-exposure prophylaxis dose is based on the regimen that was evaluated in the randomized, double-blinded, placebo-controlled trial COV-2069 in household contacts of COVID-19 patients. Analysis of data from trial COV-2069 showed statistically significant reduction in symptomatic and asymptomatic SARS-CoV-2 infection in the group receiving single dose of 600 mg of casirivimab and 600 mg imdevimab administered together subcutaneously compared to placebo. As systemic concentrations following intravenous administration are higher relative to subcutaneous administration over the first 28 days, casirivimab and imdevimab will be authorized to be administered together as subcutaneous injections or as an intravenous infusion.

The dose of 600 mg of casirivimab and 600 mg of imdevimab administered together, is expected to maintain antiviral activity against SARS-CoV-2 variants of concern and variants of interest, as defined by the CDC[11], based available pseudotyped virus-like particle assay data data.

Rationale for Repeat dose for prophylaxis
- The authorized dosing regimen for repeat dose for post-exposure prophylaxis is 600 mg of casirivimab and 600 mg of imdevimab administered subcutaneously or intravenously as loading dose followed by repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab administered monthly (or every 4 weeks) either by subcutaneous or intravenous route. Repeat dosing in certain individuals with ongoing exposure to SARS-CoV-2 is supported by pharmacokinetic data. The authorized dosing regimen is expected to produce C_{trough} values similar or higher to observed Day 28 concentrations in trial COV-2069 where the efficacy of post-exposure prophylaxis has been demonstrated.

[11] https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

- The pharmacokinetics (PK) and safety profile of the repeat dosing regimen was evaluated in a phase 1 trial COV-2093 in adult healthy subjects. The dose 600 mg casirivimab and 600 mg imdevimab was administered subcutaneously every 4 weeks for 6 doses. The safety and PK findings in this study also support the authorized repeat dosing regimen.

IV. Product Information (Presentation, Dose Preparation and Administration)

Dose Presentation

REGEN-COV (casirivimab and imdevimab) is available in two distinct presentations, as described below.

- *Dose pack bags*: Dose pack bags will include a sufficient number of vials of casivirimab and imdevimab to prepare up to two treatment doses. Casirivimab and imdevimab are each supplied in individual single use vials. Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion or injection. Imdevimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion or injection. Each REGEN-COV dose pack contains 1,200 mg of casirivimab and 1,200 mg of imdevimab.

- *Co-formulated solution of REGEN-COV*: The co-formulated solution of REGEN-COV contains two antibodies in a 1:1 ratio in a single dose vial consisting of 600 mg casirivimab and 600 mg imdevimab per 10 mL (60 mg/60 mg per mL). Co-formulated casirivimab and imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution.

Either presentation of REGEN-COV, as described above, may be prepared for intravenous infusion or subcutaneous injection. IND 148069 was referenced for this EUA amendment and contains the supporting CMC information.

Preparation and Administration Instructions – Intravenous Infusion

a) Preparation of Intravenous Infusion

Casirivimab and imdevimab solution for intravenous infusion should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials**.

2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
    - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.
3. Obtain a prefilled intravenous infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection.
4. Withdraw the appropriate amount of casirivimab and imdevimab from each respective vial(s) and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see Table 1 and Table 2).
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 (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 1: Recommended Dilution Instructions for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

<table>
<tr><th>Size of Prefilled 0.9% Sodium Chloride Infusion Bag</th><th>Preparing Using Co-Formulated Casirivimab and Imdevimab Vial</th><th>Preparing Casirivimab and Imdevimab Using Individual Vials[a]</th></tr>
<tr><td>50 mL</td><td rowspan="4">Add 10 mL of co-formulated casirivimab and imdevimab (1 vial) into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below</td><td rowspan="4">Add:
• 5 mL of casirivimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL) and
• 5 mL of imdevimab (may use 2 vials of 2.5 mL OR 1 vial of 11.1 mL)
and inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below</td></tr>
<tr><td>100 mL</td></tr>
<tr><td>150 mL</td></tr>
<tr><td>250 mL</td></tr>
</table>

[a]600 mg of casirivimab and 600 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Table 2: Recommended Dilution Instructions for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Preparing Using Co-Formulated Casirivimab and Imdevimab Vial	Preparing Casirivimab and Imdevimab Using Individual Vials[b]
50 mL	Add 5 mL of co-formulated casirivimab and imdevimab into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below	Add: • 2.5 mL of casirivimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and • 2.5 mL of imdevimab (may use 1 vial of 2.5 mL OR 1 vial of 11.1 mL) and inject into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below
100 mL		
150 mL		
250 mL		

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.
[b] 300 mg of casirivimab and 300 mg of imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.

b) Administration of Intravenous Infusion

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

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE) lined PVC, or polyurethane (PU) infusion set
  - In line or add on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the intravenous bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in line or add on 0.2 micron polyethersulfone (PES) filter (see Table 3 and Table 4). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with intravenous solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush the tubing with 0.9% Sodium Chloride Injection to ensure delivery of the required dose.

- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Table 3: Recommended Administration Rate for 600 mg of Casirivimab and 600 mg of Imdevimab for Intravenous Infusion

Size of Prefilled 0.9% Sodium Chloride Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[a]	180 mL/hr	20 minutes
100 mL	310 mL/hr	21 minutes
150 mL	310 mL/hr	31 minutes
250 mL	310 mL/hr	50 minutes

[a] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride infusion bag must be at least 20 minutes to ensure safe use.

Table 4: Recommended Administration Rate for 300 mg of Casirivimab and 300 mg of Imdevimab for Intravenous Infusion for Repeat Dosing[a]

Size of Prefilled 0.9% Sodium Chloride Infusion Bag used	Maximum Infusion Rate	Minimum Infusion Time
50 mL[b]	165 mL/hr	20 minutes
100 mL	310 mL/hr	20 minutes
150 mL	310 mL/hr	30 minutes
250 mL	310 mL/hr	49 minutes

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.
[b] The minimum infusion time for patients administered casirivimab and imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride infusion bag must be at least 20 minutes to ensure safe use.

Preparation and Administration Instructions – Subcutaneous Injection

a) Preparation of Subcutaneous Injection

Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

1. Casirivimab and imdevimab should be prepared using the appropriate number of syringes (see Table 5 and Table 6). Obtain 3 mL or 5 mL polypropylene Luer Lock syringes with luer connection and 21-gauge 1½ inch transfer needles.
2. Withdraw the appropriate amount of solution into each syringe (see Table 5 and Table 6). Prepare all syringes at the same time.
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2ºC to 8ºC (36ºF to 46ºF) for no more than 4 hours or at room temperature up to 25ºC (77ºF) for no more than 4 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 5: Preparation of 600 mg of Casirivimab and 600 mg of Imdevimab for Subcutaneous Injections

Prepare 600 mg of Casirivimab and 600 mg of Imdevimab	**Preparation of 4 Syringes**
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into FOUR separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. • **Imdevimab:** Withdraw 2.5 mL solution per syringe into TWO separate syringes. For total of 4 syringes.

Table 6: Preparation of 300 mg of Casirivimab and 300 mg of Imdevimab for Subcutaneous Injections for Repeat Dosing[a]

Prepare 300 mg of Casirivimab and 300 mg of Imdevimab	Preparation of 2 Syringes
Using Casirivimab and Imdevimab Co-formulated Vial	Withdraw 2.5 mL solution per syringe into TWO separate syringes.
Using Casirivimab and Imdevimab Individual Vials	• **Casirivimab:** Withdraw 2.5 mL solution into ONE syringe. • **Imdevimab:** Withdraw 2.5 mL solution into ONE syringe. For total of 2 syringes.

[a] Subsequent repeat dosing every 4 weeks after initial 600 mg casirivimab and 600 mg imdevimab dosing for the duration of ongoing exposure.

c) Administration of Subcutaneous Injection

- For the administration of 600 mg of casirivimab and 600 mg of imdevimab, gather 4 syringes (see Table 5) and prepare for subcutaneous injections.
- For the administration of 300 mg of casirivimab and 300 mg of imdevimab, gather 2 syringes (see Table 6) 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.
- Clinically monitor patients after injections and observe patients for at least 1 hour.

Storage

Casirivimab is preservative-free. Discard any unused portion.
Imdevimab is preservative-free. Discard any unused portion.

Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

DO NOT FREEZE. DO NOT SHAKE. DO NOT EXPOSE TO DIRECT LIGHT.

Solution in vial requires dilution prior to intraveneous infusion. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted casirivimab and imdevimab solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

The prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes in the refrigerator between 2ºC to 8ºC (36ºF to 46ºF) for no more than 4 hours or at room temperature up to 25ºC (77ºF) for no more than 4 total hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 20 minutes prior to administration.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

Background Information on the Condition

The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, approximately 191 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of July 21, 2021 including an estimated 4 million deaths. In the US, according to the CDC, as of July 21, 2021, approximately 34 million cases of COVID-19 have been reported with 609,000 deaths.

Severe illness, defined as hospitalization, admission to the intensive care unit (ICU), intubation, or mechanical ventilation or death, can occur in adults of any age with COVID-19. Adults of any age with certain underlying comorbidities or conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes, pregnancy and immunocompromised states are at increased risk for severe illness from the virus that causes COVID-19. Other medical conditions or factors also make certain individuals at high risk for progression to severe disease

(https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).

The respiratory presentation in adolescents has been similar to that in adults. The disease is typically milder in children, but a small proportion have experienced severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Götzinger et al., 2020).

Prevention Alternatives

There is no adequate, approved, and available alternative to the emergency use of casirivimab and imdevimab administered together for post-exposure prophylaxis for SARS-CoV-2 infection in patients at high risk for severe COVID-19 who are not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications), and have been exposed to someone who has COVID-19 consistent with close contact criteria according to the CDC or who are at high who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

There are currently three vaccines against COVID-19 that are authorized for emergency use:

- The Pfizer-BioNTech COVID-19 vaccine was authorized for active immunization to prevent COVID-19 in individuals 16 years of age and older on December 11, 2020. This vaccine contains nucleoside-modified messenger RNA encoding the spike glycoprotein of SARS-CoV-2 and is administered intramuscularly as a series of two doses 3 weeks apart. The EUA was expanded to include adolescents 12 years of age through 15 years of age on May 10, 2021.
- The Moderna COVID-19 vaccine was authorized for active immunization to prevent COVID-19 in individuals 18 years of age and older on December 18, 2020. This vaccine contains nucleoside-modified messenger RNA encoding the pre-fusion stabilized spike glycoprotein of SARS-CoV-2 and is administered intramuscularly as a series of two doses 4 weeks apart.
- The Janssen COVID-19 vaccine was authorized for active immunization to prevent COVID-19 in individuals 18 years of age and older on February 27, 2021. This vaccine is composed of a recombinant, replication-incompetent human adenovirus type 26 vector that expresses the spike protein in a stabilized confirmation. This vaccine is administered intramuscularly as a single dose.

COVID-19 vaccination is recommended for everyone 12 years and older for the prevention of COVID-19 in the United States.[12] The Advisory Committee on Immunization Practices (ACIP) has issued interim recommendations for the use of Pfizer-BioNTech COVID-19 vaccine (in persons ages 12 to 15 years and ages ≥16 years), Moderna COVID-19 vaccine (in persons ages ≥18 years), and Janssen (Johnson & Johnson) COVID-19 vaccine (in persons ages ≥18 years) The CDC considers a history of the following to be a contraindication to vaccination with COVID-19 vaccines:

- Severe allergic reaction (e.g. anaphylaxis) after a previous dose or to a component of the COVID-19 vaccine
- Immediate allergic reaction of any severity to a previous dose or known (diagnosed) allergy to a component of the vaccine.

Individuals with certain conditions, like solid organ transplant recipients for example, are less likely to mount humoral immune responses compared to immunocompetent individuals (Boyarsky, et al., 2021).

VI. Related Regulatory Submission(s)

Casirivimab and imdevimab have been studied in clinical trials under IND 148069. The IND trials and a separate trial not conducted under US IND are summarized in Table 4. No Drug Master Files were cross-referenced in this EUA submission (Master File holder is not applicable).

VII. Summary of Clinical Data

Table 7 provides an overview of all clinical trials evaluating REGEN-COV (casirivimab and imdevimab administered together). The data to support the authorization for post-exposure prophylaxis are from trial COV-2069. Support for the safety and pharmacokinetics of repeat subcutaneous doses administered every 4 weeks is provided by trial COV-2093.

[12] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us html

Table 7: All Clinical Trials

Study Number	IND, BLA, or Literature Reference	Type of Study (PK, Efficacy, Safety)	Population (Planned N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
COV-2069	148069	Efficacy, Safety	N=3750 Asymptomatic, healthy adults, adolescents, and pediatric subjects (<12 years) who are household contacts to an individual diagnosed with SARS-CoV-2 infection	Phase 3 randomized, double-blind, placebo-controlled trial in adults and adolescents with household contact exposure to individuals with SARS-CoV-2 infection	1200 mg SC single dose casirivimab and imdevimab (600 mg of casirivimab and 600 mg of imdevimab) 1-month efficacy assessment period; 7-month follow-up after the end of the efficacy assessment period.	Enrollment completed. (N=3270)[a]
COV-2093	148069	Safety, PK	N=940 Adult healthy volunteers	Phase 1, randomized, double- blind, placebo-controlled study in healthy adults and volunteers that have chronic but stable conditions, designed to assess the safety and tolerability of multiple subcutaneous doses of casirivimab and imdevimab	1200 mg casirivimab and imdevimab (600 mg of casirivimab and 600 mg of imdevimab) administered subcutaneously every 4 weeks for 6 doses Up to 6-month treatment period (or shorter if participant develops symptomatic SARS-CoV-2 infection); and 7-month follow-up period.	Enrollment completed. (N=969)[a]
COV-2067	148069	Efficacy, Safety	N=Phase 1: 100; Phase 2: 1300; Phase 3: 8680 Outpatient (ambulatory) adults with a positive diagnostic test for SARS-CoV-2 are enrolled in 2 cohorts: • Symptomatic cohort (mild to moderate) • Asymptomatic cohort	Phase 1/2/3, randomized, double-blinded, placebo-controlled trial in adult and adolescent ambulatory patients (i.e., outpatients) with COVID-19, including asymptomatic adults (in phase 2) with SARS-CoV-2 infection.	• 1200 mg IV single dose casirivimab and imdevimab (600 mg of casirivimab and 600 mg of imdevimab) (starting in protocol amendment 6) • 2400 mg IV single dose casirivimab and imdevimab (1200 mg of casirivimab and 1200 mg of imdevimab) • 8000 mg IV single dose casirivimab and imdevimab (4000 mg of casirivimab and 4000 mg of imdevimab) Assessments to Day 29; follow-up to Day 29 in phase 1 and 2; follow-up to Day 169 in phase 3.	Only enrolling pediatric and pregnant patients. Placebo arm stopped per IDMC recommendation. (N=9647)[b]

COV-2066	148069	Efficacy, Safety	N=Phase 1: 60; Phase 2: 631; Phase 3: 2505 Hospitalized patients enrolled in 4 cohorts: • Cohort 1A: with COVID-19 symptoms but not requiring supplemental oxygen • Cohort 1: Oxygen saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device • Cohort 2: On high-intensity oxygen therapy but not on mechanical ventilation • Cohort 3: On mechanical ventilation	Phase 1/2/3, randomized, double-blinded, placebo-controlled trial in hospitalized adult patients with COVID-19	• 2400 mg IV single dose casirivimab and imdevimab (1200 mg of casirivimab and 1200 mg of imdevimab) • 8000 mg IV single dose casirivimab and imdevimab (4000 mg of casirivimab and 4000 mg of imdevimab) Assessments to Day 29; up to 170-day follow-up in phase 1 and up to 58 days follow-up in phase 2 and 3.	Enrollment paused in Cohorts 2 and 3 for potential safety concern. Enrollment closed in Cohort 1 and 1A. (N=2156)[a]
COV-2118	148069	Vaccine interaction trial	N=180 Healthy adult volunteers who are between 18 years to 90 years of age (inclusive) who are negative at screening for both SARS-CoV-2 infection and endogenous anti-SARS-CoV-2 antibodies.	Phase 2, randomized, open-label, parallel group study to assess the immunogenicity, safety, and tolerability of the Moderna mRNA-1273 vaccine administered with casirivimab and imdevimab. Subjects will be enrolled in Wave 1 (2:2:2:1 randomization) or Wave 2 (2:2:1 randomization)	Wave 1: Arm 1: • REGEN-COV: 1200 mg IV day 1 • mRNA-1273: day 15 and day 43 Arm 2: • REGEN-COV: 300 mg IV day 1 • mRNA-1273: day 15 and day 43 Arm 3: • REGEN-COV:150 mg IV day 1 • mRNA-1273: day 15 and day 43 Arm 6a: • REGEN-COV: none • mRNA-1273: day 15 and day 43 Wave 2: Arm 4: • REGEN-COV: 1200 mg IV day 1 • mRNA-1273: day 1 and day 29 Arm 5: • REGEN-COV: 600 mg IV day 1 • mRNA-1273: day 1 and day 29 Arm 6b: • REGEN-COV: none • mRNA-1273: day 1 and day 29	Ongoing
COV-20145	148069	Dose-finding trial	N=1400 Adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2.	Randomized, double-blind, placebo-controlled, parallel group study to assess the dose response of single	In the IV single dose cohort, patients were randomized 2:2:2: 2:1 to: • 2400 mg (1200 mg per mAb) • 1200 mg (600 mg per mAb) • 600 mg (300 mg per mAb) • 300 mg (150 mg per mAb) • Placebo IV single dose	Enrollment closed in February 2021 (N=1149)[a]

				intravenous or single subcutaneous dosing in outpatients with SARS-CoV-2 infection.	In the subcutaneously administered single dose cohort, patients were randomized 2:2:1 to: • 1200 mg (600 mg per mAb) • 600 mg (300 mg per mAb) • Placebo SC single dose Assessments to Day 29; 170-day follow-up	
(b) (4)						
RECOVERY Trial	Non-IND	Efficacy, Safety	Hospitalized adults and children ages 12 years and older	Phase 3, open-label trial in patients hospitalized with COVID-19 comparing the effects of adding REGN-COV2 to the usual standard-of-care versus standard-of-care on its own.	• 8000 mg IV single dose casirivimab and imdevimab (4000 mg of casirivimab and 4000 mg of imdevimab)	Enrollment closed in June 2021 (N=9785)[c]

Sources: Adapted from Applicant's submission to EUA 91 dated June 17, 2021 entitled 'EUA 000091 Response to IR'; https://www.recoverytrial.net/ accessed on June 17, 2021

Abbreviations: COVID-19 = coronavirus disease 2019; IND = investigational new drug; IV = intravenous; N = number of participants; BLA = Biologics License Application; PK = pharmacokinetics; IV = intravenous; SC = subcutaneous; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] N reflects the total number of subjects randomized and treated with REGEN-COV or placebo

[b] N reflects the total number of subjects randomized and treated with REGEN-COV or placebo in the completed portions of study; this number does not include pregnant and pediatric patients

[c] N reflects the total number of subjects randomized to REGEN-COV or usual care alone

VIII. Clinical Efficacy

The topline results from 2475 subjects in the completed phase 3 prophylaxis trial, COV-2069 (NCT04452318), provide support for efficacy and safety of a single dose of REGN-COV (casirivimab and imdevimab administered together) for post-exposure prophylaxis of SARS-CoV-2 infection.

Design

COV-2069 is a randomized, double-blind, placebo-controlled trial in household contacts with close exposure to a household member known to be infected with SARS-CoV-2 (index case) but who were themselves asymptomatic. The study consists of four cohorts based on subjects' age and baseline SARS-CoV-2 quantitative RT-PCR (RT-qPCR) status, as follows:

- Cohort A: adult and adolescent subjects (≥12 years of age) who are SARS-CoV-2 RT-qPCR negative at baseline
- Cohort B: adult and adolescent subjects (≥12 years of age) who are SARS-CoV-2 RT-qPCR positive at baseline
- Cohort A1: pediatric subjects <12 years of age who are SARS-CoV-2 RT-qPCR negative at baseline
- Cohort B1: pediatric subjects <12 years of age who are SARS-CoV-2 RT-qPCR positive at baseline

Eligible subjects were randomized 1:1 to REGEN-COV 1200 mg (600 mg of casirivimab and 600 mg of imdevimab given together) or placebo administered subcutaneously. The assigned study treatment was administered within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample. Assessments included weekly SARS-CoV-2 RT-qPCR testing by nasopharyngeal swabs, weekly interviews with the investigator for assessment of COVID-19 symptoms and assessment of adverse events through study day 29, which is denoted as the efficacy assessment period (EAP); and follow-up until day 229.

Primary endpoint

- Cohort A: Proportion of subjects who have symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
- Cohort B: Proportion of subjects who subsequently develop signs and symptoms (broad term) within 14 days of a positive RT-qPCR at baseline or during the EAP.

Symptomatic infection was defined using 'broad term', 'strict term', or CDC[13] definitions, as shown below .

- *Broad term* defined as any of the following symptoms: fever, sore throat, cough, shortness of breath/difficulty breathing, chills, nausea, vomiting, diarrhea, headache, red or watery eyes, body aches such as muscle pain or joint pain, loss of taste/smell, fatigue, loss of appetite or poor eating/feeding, confusion, dizziness, pressure/tightness in chest, chest pain, stomach ache, rash, sneezing, runny nose, sputum/phlegm.
- *Strict term* defined by: fever PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath), OR 2 respiratory symptoms, OR 1 respiratory symptom PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise).
- *CDC's definition* is the presence of: at least 2 of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion or runny nose OR any 1 of the following symptoms: cough, shortness of breath, difficulty breathing, new olfactory disorder, new taste disorder OR severe respiratory illness with at least 1 of the following, clinical or radiographic evidence of pneumonia, acute respiratory distress syndrome (ARDS).

Analysis sets

The Applicant conducted independent analyses for each Cohort A and B. Results from Cohort A1 and B1 in subjects <12 years are not submitted. In both cohorts A and B, the pre-specified efficacy analysis set was the seronegative modified full analysis set (seronegative mFAS). As the study populations in the two cohorts were different, the definition of seronegative mFAS varied. The analysis datasets for Cohorts A and B are shown in Table 8; and the definition of seronegative mFAS in each cohort is provided below:

- In Cohort A, seronegative mFAS-A included all randomized subjects aged 12 years and older who had a central laboratory-confirmed negative test for SARS-CoV-2 RT-qPCR and negative serology at baseline.

- In Cohort B, seronegative mFAS-B included all randomized subjects ages 12 years and older who had a central-laboratory confirmed positive test for SARS-CoV-2 RT-qPCR, negative serology and were asymptomatic at baseline.

SARS-CoV-2 serology status was determined by the following assays: EuroImmun ELISA (IgG), EuroImmun ELISA (IgA) and Abbott Architect (IgG).

[13] COVID-19 2020 Interim Case Definition, Approved August 5, 2020
https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/08/05/

The Applicant's analyses included subjects who were randomized and treated in Cohorts A and B on or before January 28, 2021 (as shown in Table 8). Of note, the efficacy analysis excluded 554 subjects who were in the initial administrative analysis conducted previously.

Table 8: Safety and Efficacy Analysis Datasets, COV-2069

Analysis set	Cohort A RT-qPCR negative			Cohort B RT-qPCR positive		
	Placebo	REGEN-COV	Total	Placebo	REGEN-COV	Total
Safety analysis dataset: Randomized and treated	1306	1311	2617	156	155	311
Efficacy analysis dataset: Randomized, treated, and seronegative (seronegative mFAS)	752	753	1505	104	100	204

Source: EUA 91 Amendment Table 14.3.1
REGEN-COV = 600 mg of casirivimab and 600 mg of imdevimab administered together

Demographics and Baseline Characteristics

Cohort A

The key demographic and baseline disease characteristics were generally well balanced in the REGEN-COV and placebo groups in the seronegative FAS (Table 9). The key demographic and baseline characteristics were generally similar between the seronegative FAS and all randomized and treated population in Cohort A. In the seronegative FAS-A, approximately 38% of the subjects were 50 years or older, 54% were women, 9% were Black, and 41% were of Hispanic or Latino ethnicity. At baseline, 76% of subjects in each group had at least one high risk factor for severe COVID-19 and/or hospitalization, as defined currently in the EUA Fact Sheet for Healthcare Providers (≥65 years of age, BMI ≥25 kg/m^2, BMI ≥85th percentile for their age and gender if age 12-17 years, pregnancy, chronic kidney disease, diabetes, immunosuppressive disease, currently receiving immunosuppressive treatment, cardiovascular disease or hypertension, chronic pulmonary disease, sickle cell disease, neurodevelopmental disorders, or having a medical-related technological dependence). The household size was generally well-balanced between the treatment arms, with approximately 82% of the households including one subject within the household.

Table 9: Demographics and Selected Baseline Characteristics in Cohort A (seronegative mFAS-A)

	REGEN-COV (N=753)	Placebo (N=752)	Total (N=1505)
Mean age (SD)	43 (16)	43 (16)	43 (16)
Age (years)			
≥ 50	294 (39%)	280 (37%)	574 (38%)
≥ 12 to < 18	34 (5%)	34 (5%)	68 (5%)
≥ 18 to < 65	643 (85%)	663 (88%)	1306 (87%)
≥ 65	76 (10%)	55 (7%)	131 (9%)
Female	420 (56%)	394 (52%)	814 (54%)
Race: White	653 (87%)	635 (84%)	1288 (86%)
Race: Black/African American	62 (8%)	78 (10%)	140 (9%)
Hispanic or Latino	291 (39%)	319 (42%)	610 (41%)
BMI ≥30 kg/m^2	261 (35%)	250 (33%)	511 (34%)
High risk based on (current) EUA criteria	570 (76%)	567 (75%)	1137 (76%)
Number of households	679	686	1209
Median number of household size	3	3	3
Number of households by size			
1	486/679 (72%)	503/686 (73%)	989/1209 (82%)
2	146/679 (22%)	136/686 (20%)	172/1209 (14%)
3	30/679 (4%)	30/686 (4%)	31/1209 (3%)
4	13/679 (2%)	13/686 (2%)	13/1209 (1%)
≥ 5	4/679 (1%)	4/686 (1%)	4/1209 (<1%)

Source: EUA 91 Amendment Tables 14.4.1.1 and 14.4.3.3.1 in 2069-tfl-tables.pdf and EUA Regulatory Response submitted on 18 June, 2021
REGEN-COV = 600 mg of casirivimab and 600 mg of imdevimab administered together

Results

The pre-specified primary analysis set in Cohort A was the seronegative mFAS-A and these findings are presented below. Results for the subgroup of seronegative mFAS-A subjects who were at high risk for severe COVID-19 are presented as well. As serology results may not be readily available to healthcare providers, the analysis for all subjects who were RT-qPCR negative at baseline, regardless of serology status is provided.

i) Seronegative mFAS-A

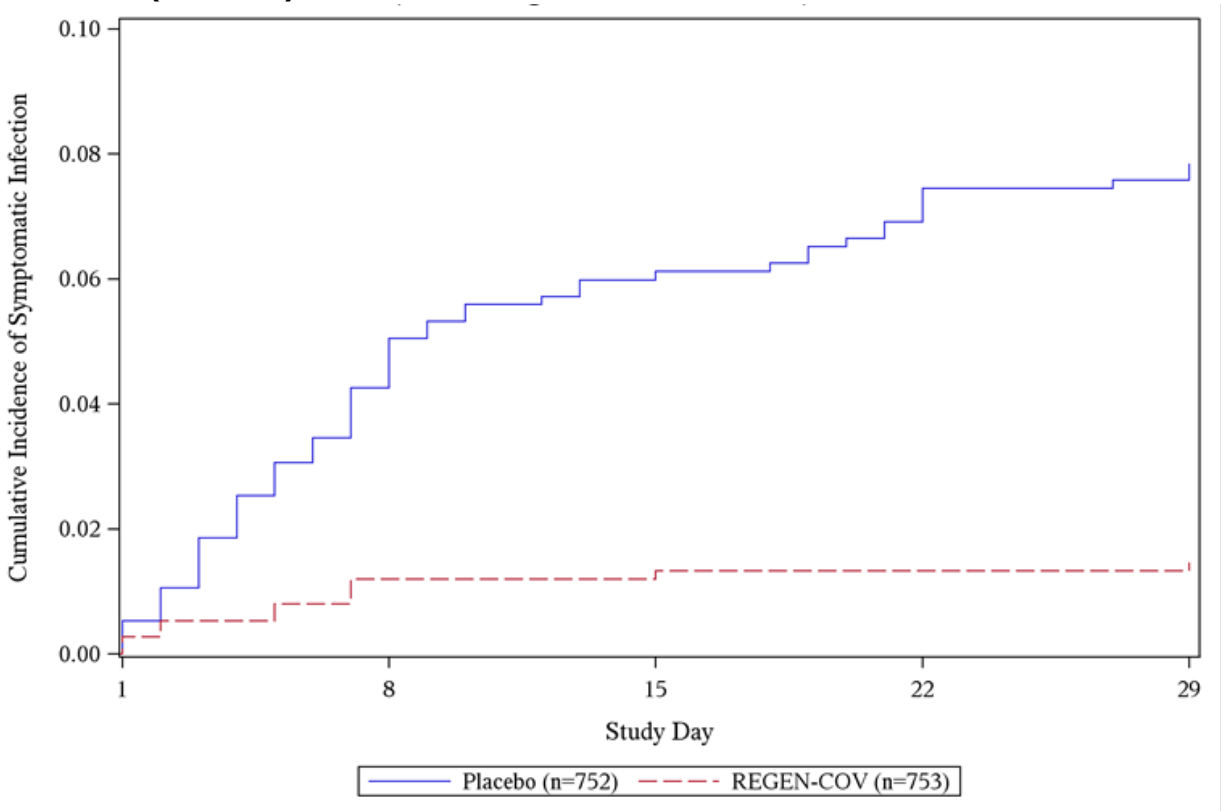
As shown in Table 10, REGEN-COV resulted in statistically significant reduction in symptomatic infections during the EAP among the patients in the seronegative mFAS-A regardless of definition of symptomatic infection. With the broad term definition, there was an 81% risk reduction in symptomatic SARS-CoV-2 infection with REGEN-COV treatment versus placebo [11/753 (1%) and 59/752 (8%); adjusted odds ratio 0.17; p<0.0001]. Figure 1 shows the cumulative incidence of symptomatic infection (broad term) through Day 29.

Table 10: Proportion of Subjects with Symptomatic Infection During EAP in Cohort A (mFAS-A)

Definition of symptomatic infection	REGEN-COV (N=753)	Placebo (N=752)	Relative Risk Reduction (95% CI) P-value	Odds Ratio (95% CI) P-value[1]
Broad term[2]	1.5% (11)	7.8% (59)	81.4% (64.8%, 90.1%) P<0.0001	0.17 (0.09, 0.33) P<0.0001
CDC definition	0.8% (6)	6.1% (46)	87.0% (69.7%, 94.4%) P<0.0001	0.12 (0.05, 0.29) P<0.0001
Strict term	0.3% (2)	2.9% (22)	90.9% (61.5%, 97.9%) P<0.0001	0.09 (0.02, 0.37) P=0.0010

[1]Odds ratio, 95% CI, and p-value were adjusted by age (≥ 12 to < 50 vs ≥ 50 years) and region (US vs non-US)
[2]Infections were RT-qPCR positive either by central lab, or by local lab (only one subject in placebo arm)
Source: EUA 91 Amendment Tables 14.6.1.1, 14.6.1.2.1, 14.6.2.2.1, 14.6.2.2.2, 14.6.2.2.4 and 14.6.2.2.5 in 2069-tfl-tables.pdf and statistical reviewer
REGEN-COV = 600 mg of casirivimab and 600 mg of imdevimab administered together

Figure 1: Cumulative Incidence of Symptomatic Infection (Broad Term) in Cohort A (mFAS-A)



Source: EUA 91 Amendment Figure 2 in clin-info-amend.pdf
REGEN-COV = 600 mg of casirivimab and 600 mg of imdevimab administered together

In addition, there was a 66% risk reduction in the proportion of participants with any RT-qPCR-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic) with REGEN-COV treatment compared to placebo [36/753 (5%) vs. 107/752 (14%); odds ratio adjusted by age and region: 0.31; p<0.0001].

ii) Seronegative mFAS-A: high risk for severe COVID-19

In patients at high risk for progression to severe disease (based on current EUA high risk criteria), there was a lower incidence of sympomatic infections in the REGEN-COV arm compared to placebo.

Approximately 76% of seronegative mFAS-A subjects (1137/1505) were at high risk for progression to COVID-19. Among these, 68% met the BMI high risk criteria, 22% had cardiovascular disease or hypertension, 9% were at least 65 years of age, with other risk factors present less frequently. In high risk subjects, there was a 76% risk reduction in symptomatic COVID-19 infection (broad term) with REGEN-COV compared to placebo [10/570 (2%) vs 42/567 (7%); odds ratio 0.22; p value <0.0001]. There was one COVID-19-related hospitalization in the placebo group; there were no COVID-19-related hospitalizations in the REGEN-COV group. There were no deaths in either the REGEN-COV or placebo groups.

iii) All RT-qPCR negative subjects, regardless of serology status

In subjects who were RT-qPCR negative at baseline, regardless of serology status, an 82% reduction in the rate of symptomatic infections (broad term) was observed compared to placebo (adjusted odds ratio 0.17; p-value < 0.0001) (see Table 11).

Table 11: Proportion of Subjects with Symptomatic Infection (broad term) During EAP in Cohort A (All Randomized and Central-Lab-Confirmed RT-qPCR Negative at Baseline, regardless of serology status)

REGEN-COV (N=1046)	Placebo (N=1021)	Relative Risk Reduction (95% CI) P-value	Odds Ratio (95% CI) P-value[1]
12 (1.1%)	66 (6.5%)	82.3% (67.4%, 90.3%) P<0.0001	0.17 (0.09, 0.31) P<0.0001

[1]Odds ratio, 95% CI and p-value were adjusted by age (≥ 12 to < 50 vs ≥ 50 years) and region (US vs non-US).
Source: EUA 91 Amendment Table 14.6.2.3.66, 14.6.2.3.67 in 2069-tfl-tables.pdf and statistical reviewer
REGEN-COV = 600 mg of casirivimab and 600 mg of imdevimab administered together

It is useful to estimate the impact of an intervention by estimating the number needed to treat to prevent an event. The estimated differences in event rates for 'broad term' symptomatic infections in the REGEN-COV and placebo groups in Table 11 (above) correspond to a number needed to treat of 18 (95% CI [14, 27]).

Adolescents (12 and older) subgroup

In the adolescent subgroup, the trends were similar to those observed in the overall population. The incidence of symptomatic SARS-CoV-2 infections (broad term) during the EAP among adolescents in Cohort A, regardless of serology status, was 0 (0/46) and 9% (4/43) in the REGEN-COV and placebo groups, respectively.

Cohort B

Cohort B included subjects who were RT-qPCR positive at baseline and were asymptomatic. The key demographic and baseline disease characteristics were generally well balanced in the casirivimab and imdevimab, and placebo groups among all randomized subjects in Cohort B.

In the primary analysis population consisting of subjects who were PCR-positive and seronegative at baseline, a 31% reduction in the rates of symptomatic infection using the broad term definition was observed with casirivimab and imdevimab compared to placebo during efficacy assessment period (odds ratio adjusted by age and region: 0.54 with 95% CI [0.30, 0.97]; p-value=0.038). COVID-19 related emergency room visits or hospitalizations were observed in zero (0/155) and 4% (6/156) subjects in the casirivimab and imdevimab and placebo arms, respectively. These trends favor an effect of casirivimab and imdevimab on important clinical endpoints; although we note that only 32% of the Cohort B population was at high risk for developing severe COVID-19, including hospitalization and death.

In all Cohort B subjects (i.e., PCR-positive) regardless of baseline serology status, the treatment differences for REGEN-COV versus placebo did not demonstrate clinical or nominal significance for the endpoint of reduction in the incidence of COVID-19 related hospitalization or death (REGEN-COV 0% [0/155] and placebo 2% [3/156]), which are clinically important endpoints in the context of a treatment indication for an EUA. In the seronegative population, these results were also not significant at the two-sided 0.05 significance level (REGEN-COV 0% [0/100] and placebo 3% [3/104]).

SEE ATTACHED ADDENDUM

Combined Cohort A and Cohort B

In a post-hoc analysis of combined Cohort A and Cohort B data in COV-2069, regardless of serology status, a nominally significant reduction of 62% in COVID-19 was observed with REGEN-COV compared to placebo [46/1201 (4%) vs 119/1177 (10%); adjusted odds ratio 0.35, p<0.0001].

Efficacy Summary

Post-exposure prophylaxis

A statistically significant 81% reduction in the risk of COVID-19 was observed with REGEN-COV treatment (1%) compared to placebo (8%) in RT-qPCR negative and seronegative subjects (the primary analysis population) living in households with SARS-CoV-2-infected cases in COV-2069. Statistically significant reductions in any SARS-CoV-2 infection (symptomatic or asymptomatic RT-qPCR confirmed infection) was also observed. In a post-hoc analysis in the subgroup that met the criteria for high risk for progression to severe COVID-19, as defined in the EUA Fact Sheet, there was a 76% risk reduction in COVID-19 with REGEN-COV (2%) compared to placebo (7%) which was significant. A similar trend favoring REGEN-COV was observed in the adolescent subgroup.

In an outbreak setting, we anticipate that prophylaxis will be administered based on confirmed exposure or based on a high suspicion of exposure to SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) in the absence of RT-PCR testing results. A nominally significant reduction of 62% in the rate of symptomatic infection was observed with REGEN-COV compared to placebo in post-hoc analysis of combined Cohort A and Cohort B data. The overall data from COV-2069 support the clinical benefit of 600 mg of casirivimab and 600 mg of imdevimab administered as a single dose subcutaneously for post-exposure prophylaxis of COVID-19.

(b) (4)

In COV-2069 Cohort B with RT-qPCR positive and asymptomatic subjects at baseline, statistically significant reduction of 31% in RT-qPCR confirmed symptomatic infection was observed with REGEN-COV compared to placebo. Fewer COVID-19-related hospitalizations and ER visits were observed in the REGEN-COV arm compared to placebo; however, the differences were not significant. COVID-19 hospitalization or death endpoints are clinically important endpoints for assessing the effects on treatment of ambulatory nonhospitalized patients in the context of an EUA; and the findings from Cohort B do not support extending the current EUA (b) (4) .

IX. Clinical Safety

The safety data supporting the post-exposure prophylaxis authorization is from approximately 2,000 subjects who received casirivimab and imdevimab administered together subcutaneously primarily in the phase 3 trial COV-2069 with additional supporting safety data for repeat dosing from a phase 1 trial COV-2093. Overall, approximately 16,000 clinical trial participants, both non-

hospitalized and hospitalized, have received REGEN-COV intravenously as single doses. Approximately 700 subjects received repeat dosing of 600 mg of casirivimab and 600 mg of imdevimab administered subcutaneously every four weeks for 24 weeks in COV-2093.

Exposure for Safety Analysis

In COV-2069, the safety analysis dataset included all subjects who were randomized and treated in Cohorts A and B. Cohort A (i.e., subjects who were RT-qPCR negative at baseline) consisted of 1311 and 1306 subjects in the REGEN-COV and placebo arms, respectively. Overall, the median duration of follow-up was 15 weeks (1-33 weeks) with 92% of subjects completing at least 8 weeks of follow-up at the analysis cut-off timepoint. Cohort B dataset (i.e., infected subjects who were RT-qPCR positive at baseline and asymptomatic) consisted of 155 and 156 subjects in the REGEN-COV and placebo arms, respectively. Overall, the median duration of follow-up was 14 weeks (3-34 weeks) with 91% of subjects completing at least 8 weeks of follow-up at the analysis cut-off timepoint.

In the phase 1 trial COV-2093, the safety dataset consisted of 729 and 240 subjects in the REGEN-COV and placebo arms, respectively. The mean observation period for the analysis was 24 weeks.

Trial COV-2069

In Cohort A, treatment emergent adverse events were observed in fewer subjects in the REGEN-COV arm compared to placebo (20% vs 29%), as shown in Table 12. The majority of treatment-emergent adverse events (TEAEs) were grade 1 or 2 in severity. Grade 3 or 4 TEAEs were observed in fewer subjects in the REGEN-COV arm compared to placebo (1% vs 2%). There were 2 deaths in each treatment arm (<1%). Serious adverse events (SAEs) were observed in 1% of subjects in each arm. There no were discontinuations due to adverse events in Cohort A.

Table 12: Overview of Treatment-Emergent Adverse Events, Cohort A COV-2069, overall study period

	Casirivimab 600 mg and imdevimab 600 mg subcutaneous (N=1311)	**Placebo subcutaneous (N=1306)**
Subjects with at least one TEAE	265 (20%)	379 (29%)
Deaths	2 (<1%)	2 (<1%)
Serious adverse events	10 (1%)	15 (1%)
Discontinuations due to AE	0	0
Grade 3 or 4 TEAEs	11 (1%)	22 (2%)

Source: Table 14.7.1.1.c 2069-tfl-tables.pdf
TEAE=treatment emergent adverse event; AE=adverse event

Similarly, in Cohort B, TEAEs were observed in fewer subjects in the REGEN-COV arm compared to the placebo arm (34% vs 48%). The majority of TEAEs were grade 1 or 2 in severity; with Grade 3 or 4 TEAEs observed in fewer subjects in the REGEN-COV arm (1%) compared to the placebo arm (3%). There were no deaths, or discontinuations due to adverse events; and no SAEs were observed in the REGEN-COV arm compared to 3% of subjects in the placebo arm.

Treatment Emergent Adverse Events

In Cohort A, injection site reactions and COVID-19-related AEs were the most frequently occurring events in the REGEN-COV arm (Table 13). Injection site reactions occurred in 4% and 2% of subjects in the REGEN-COV and placebo arm, respectively. These ISR events are discussed in more detail below. There were fewer COVID-19 AEs and asymptomatic COVID-19 AEs in the REGEN-COV arm compared to the placebo arm (we surmise that the preferred term 'asymptomatic COVID-19' refers to asymptomatic SARS-CoV-2 infection cases). The remaining TEAEs occurring in at least 2% of subjects in either treatment arm were headache and urinary tract infection; and each AE occurred less frequently in the REGEN-COV arm compared to the placebo arm.

Table 13: Proportion of subjects with Treatment Emergent Adverse Events in at least 2% in any arm in Cohort A, COV-2069

	Casirivimab 600 mg and imdevimab 600 mg subcutaneous (N=1311)	**Placebo subcutaneous (N=1306)**
Subjects with at least one TEAE	265 (20%)	379 (29%)
Preferred Term		
Injection site reaction	55 (4%)	19 (2%)
Asymptomatic COVID-19	54 (4%)	108 (8%)
COVID-19	15 (1%)	112 (9%)
Headache	24 (2%)	46 (4%)
Urinary tract infection	14 (1%)	19 (2%)

Source: Table 14.7.1.2.1c SAF-A 2069-tfl-tables.pdf
TEAE=treatment emergent adverse event

In Cohort B, TEAEs occurring in at least 2% of subjects were COVID-19 (22% REGEN-COV vs 31% placebo), and asymptomatic COVID-19 (5% REGEN-COV vs 8% placebo), and injection site reactions (4% REGEN-COV and 1% placebo).

Deaths

There were 4 deaths in the overall trial through the data analysis cut-off timepoint, including 2 deaths in each treatment arm. All four deaths were in

Cohort A. In the REGEN-COV arm, the AEs leading to death were congestive cardiac failure (n=1) and sudden death (n=1). Both AEs occurred in the follow-up period after study day 29, on days 59 and 80 after dose administration. Each of these events was assessed by the investigator as not related to study treatment or COVID-19. In the placebo arm, the AEs leading to death were cardiac arrest (n=1) and gunshot wound (n=1). The AEs occurred in the follow-up period, after study day 29, on days 45 and 55 after dose administration; and each of these events was assessed by the investigator as not related to study treatment or COVID-19.

Serious Adverse Events

In Cohort A, 25 SAEs were reported in 10 subjects (1%) and 15 subjects (1%) in the REGEN-COV and placebo arms, respectively. All SAEs were assessed to be unrelated to study treatment. In the REGEN-COV arm, no SAE occurred in 2 or more subjects. In the placebo arm, SAEs occurring in at least 2 subjects were COVID-19 (n=4) and COVID-19 pneumonia (n=2); and the remaining SAEs occurred in one subject each. In Cohort B, no SAEs occurred in the REGEN-COV arm compared to four SAEs in 4 (3%) subjects in the placebo arm. The SAEs in the placebo arm were COVID-19 (n=2), COVID-19 pneumonia (n=1), and acute pancreatitis (n=1).

Discontinuations due to AEs

No subjects withdrew from the trial due to TEAEs.

Analysis of Submission-Specific Safety Issues

Injection Site Reactions

In the overall trial including both Cohorts A and B, symptoms which constituted ISRs were observed in more subjects in the REGEN-COV group (61/1493 subjects or 4%) compared to the placebo group (20/1509 or 1%). All ISRs were grade 1 or 2 in severity; with no grade 3 or 4 events. The most common ISR events in at least 1% of subjects in any group were erythema (2% REGEN-COV vs 1% placebo), pruritus (1% REGEN-COV vs <1% placebo), ecchymosis (1% REGEN-COV vs <1% placebo), and edema (1% REGEN-COV vs <1% placebo).

Hypersensitivity Reactions and Anaphylaxis

In the overall trial, including both Cohorts A and B, hypersensitivity reactions occurred in 1% of subjects in the REGEN-COV arm (9/1493 subjects) and the placebo arm (21/1509 subjects). All hypersensitivy reactions were grade 1 or 2 in severity. There were no grade 3 or 4 hypersensitivity reactions, and no anaphylaxis events.

Rash was the only hypersensitivity AE observed in at least 2 subjects in any treatment arm; with the remaining AEs occurring in one subject each. The AEs assessed as related to study treatment in the REGEN-COV arm were throat tightness (n=1; grade 1; onset on day 2) and pruritus (n=1; grade 1; onset on day 1); both these events had resolved by day 8. The majority of events resolved without medical management; but 3 subjects in the REGEN-COV arm required medication, including analgesic and antihistamines.

Trial COV-2093

Additional safety with subcutaneous administration of REGEN-COV (600 mg of casirivimab and 600 mg of imdevimab) was submitted from trial COV-2093 (NCT# 04519437), a randomized double-blind, placebo-controlled trial evaluating the safety and pharmacokinetic profile in adult healthy volunteers. Specifically, the safety profile of repeat subcutaneous doses administered every 4 weeks for 24 weeks was evaluated in the 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. Similar to COV-2069 discussed previously, the most common TEAEs were injection site reactions (ISRs); which were observed in 35% and 16% of subjects with repeat dosing in the casirivimab and imdevimab and placebo arms, respectively. Apart from ISRs, commonly occurring TEAEs observed in at 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).

Deaths, Serious Adverse Events, and Discontinuations due to AEs

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 occurred in 4 subjects, including 3 subjects in the REGEN-COV arm (<1%) and 1 subject in the placebo arm (<1%). 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.

Injection site reactions, Hypersensitivity reactions and Anaphylaxis

Injection site reactions were observed in 12% and 4% of subjects in the casirivimab and imdevimab and placebo arms, respectively, with single dose. The ISRs 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). With repeat dosing, ISRs were observed in 35% and 16% of subjects in the REGEN-COV and placebo arms. The incidence of ISRs increased with repeat dosing, specifically with the fifth and sixth dose (see Table 14). The reason for the observed higher rate of ISRs with dose #5 or #6 is not completely understood at this time.

Table 14: 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

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, with a median time of 2.0 days (1-43 days) in the REGEN-COV arm and 2.5 days (1-16 days) in placebo arm. Hypersensitivity reactions occurred in 8 subjects (1%) in the REGEN-COV group and all hypersensitivity reactions were grade 1 or 2 in severity. There were no grade 3 or 4 hypersensitivity reactions or anaphylaxis events in the trial. The majority of the grade 1 or 2 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.

Other Safety-related Issues

Anti-Drug Antibodies

The Applicant provided data from study COV-2093, which showed the incidence of baseline immunogenicity with casirivimab and imdevimab was low (approximately 3%) and similar to placebo. Anti-drug antibody (ADA) titer and neutralizing antibody (NAb) analyses are in progress. The effect of ADA after a single dose of 600 mg casirivimab and 600 mg imdevimab on PK, efficacy and safety are currently unknown.

Antibody-Dependent Enhancement of Infection

To date, there are no compelling data to support the occurrence of antibody-dependent enhancement (ADE) of infection following administration of casirivimab and imdevimab when administered together (please see Section XIII, Nonclinical Data to Support Efficacy for more information related to ADE).

Safety summary

Overall, approximately 16,000 subjects have been exposed to REGEN-COV (casirivimab and imdevimab) in clinical trials in hospitalized and non-hospitalized subjects. Approximately 13,500 subjects received intravenous infusions and 2,500 subjects received subcutaneous injections in the clinical program including in other trials not described in this review. In addition to the safety concerns identified with intravenous administration for the authorized treatment indication, injection site reactions were identified as concerns specific to the subcutaneous route of administration. Local erythema was the most commonly occuring injection site reaction; and all injection site reactions were mild to moderate in severity. Hypersenstivity reactions were observed with single dose of REGEN-COV administered subcutaneously. All hypersensitivity reaction events were mild to moderate in severity. While most events did not require medical management, a few cases required medical attention and administration of antihistamines and analgesic medications. Based on all the currently available safety data, a post-dose observation period of at least one hour is recommended for post-exposure prophylaxis.

Additional safety concerns were not identified with repeat dosing at monthly intervals. Specific to this authorization for repeat dosing in the setting of prophylaxis, previously demonstrated severe hypersensitivity reactions, including anaphylaxis to REGEN-COV, will be a contraindication.

X. Specific Populations

Rationale for Inclusion of Adolescent Patients under EUA

As of June 10, 2021, over 4 million cases of COVID-19 have been reported in children in the United States, Puerto Rico, and Guam (https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/). Children represent

approximately 13% of all COVID-19 cases in the US. While COVID-19 is typically milder in children, some pediatric patients require hospitalization and ICU-level care (Götzinger et al. 2020). Given that COVID-19 can be a serious and life-threatening disease in adolescent patients (particularly in those with risk factors for the development of severe illness and hospitalization), the similarities in physiology to adults, the expected similar PK in adolescents weighing ≥40 kg, and the safety profile, there is a prospect of benefit for this population. Note that vaccines are authorized for adolescents. Adolescents were included in COV-2069; and findings in this age group are supportive of clinical benefit and no specific safety concern was identified in the adolescent subgroup.

Based on the totality of evidence to support the prospect of benefit and because it is reasonable to believe the known and potential benefits outweigh the known and potential risks, the authorization of casirivimab and imdevimab administered together for post-exposure prophylaxis of COVID-19 should also include adolescents who are 12 years of age and older and who weigh at least 40 kg.

Dosing Considerations for Specific Populations

- No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are older than 12 years of age. Casirivimab and imdevimab is not recommended for pediatric patients weighing less than 40 kg or those less than 12 years of age.
- Limited safety data are available from pediatric patients who weigh at least 40 kg and are older than 12 years of age, pregnant women, lactating women, patients with renal insufficiency, or patients with hepatic insufficiency. Safety and PK data are not available in children <12 years. No dosage adjustment is recommended based on renal impairment, during pregnancy or while lactating. The effect of other covariates (e.g., age, sex, race, body weight, disease severity) on PK of casirivimab and imdevimab is unknown.
- Nonclinical reproductive toxicology studies with casirivimab and imdevimab have not been conducted.
- No binding of clinical concern was seen with either casirivimab or imdevimab in a tissue cross-reactivity study in select human fetal tissues.
- No specific risks to pregnant or lactating women have been identified based on the nonclinical safety data.

XI. Clinical Pharmacology

Pharmacokinetics

A summary of pharmacokinetic (PK) parameters after a single 1200 mg IV dose (600 mg of casirivimab and 600 mg of imdevimab) and a single 1200 mg

subcutaneous dose (600 mg of casirivimab and 600 mg of imdevimab) is provided in Tables 15 and 16.

Table 15: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 600 mg of Casirivimab and 600 mg of Imdevimab Intravenous Dose of REGEN-COV in 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
[3] observed concentration 28 days after dosing, i.e., on day 29, as defined in the protocol

Table 16: Summary of PK Parameters for Casirivimab and Imdevimab After a Single 600 mg of Casirivimab and 600 mg of Imdevimab Subcutaneous Dose of REGEN-COV in Study COV-2069

PK Parameter[1,5]	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
[5] Mean (SD) concentration at 24 hours (C_{24}) of casirivimab and imdevimab in serum with 1200 SC dosing, 22.5 (11.0) mg/L and 25.0 (16.4) mg/L, respectively

After six repeated 600 mg of casirivimab and 600 mg of imdevimab subcutaneous (SC) doses given once-monthly in Study 2093, steady-state was approximately reached at the end of the sixth dosing interval with an accumulation ratio of ~2 for both casirivimab and imdevimab.

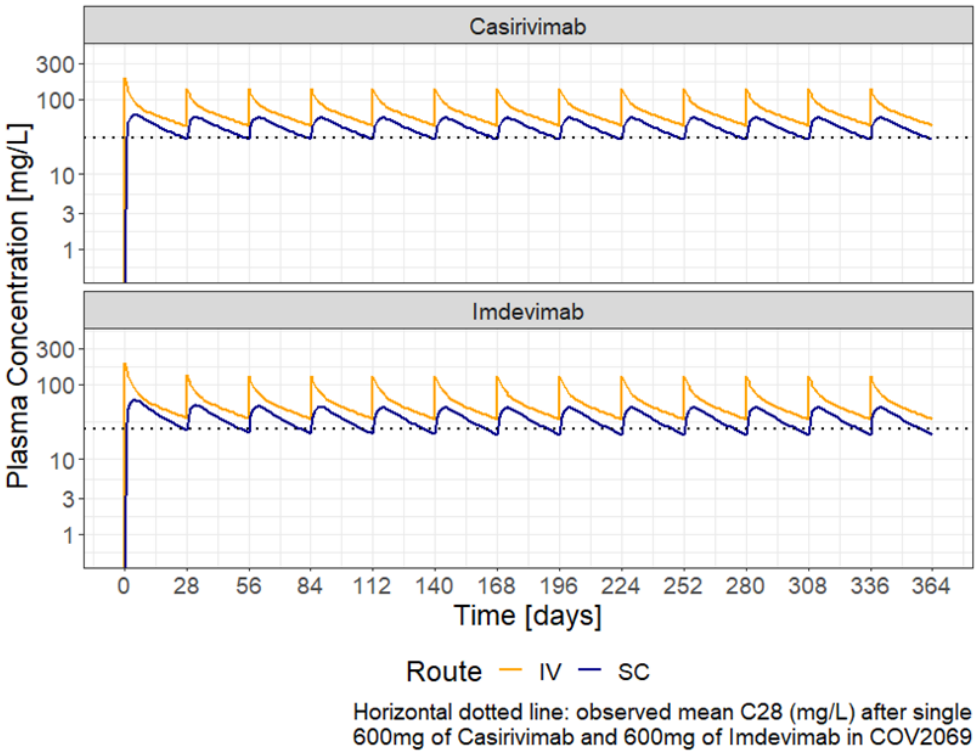
The simulated exposures of casirivimab and imdevimab with the proposed dosing regimen for repeat-dosing prophylaxis are shown in Table 17 and Figure 2. The results of these simulations show that predicted Ctrough of casirivimab and imdevimab in serum for repeat dosing is similar to the observed mean day 28 concentrations in serum for the single 1200 mg SC dose in study COV-2069.

Table 17: Predicted Mean Serum Concentration for Casirivimab and Imdevimab at Day 28, 56, and Steady State after a Loading Dose of 600 mg of Casirivimab and 600 mg of Imdevimab Followed by Monthly (Every 4 Weeks) Maintenance Doses of 300 mg of Casirivimab and 300 mg of Imdevimab

Predicted Mean Concentration (mg/L)						
	C_{Day28}		C_{Day56}		$C_{trough,ss}$	
	Casirivimab	Imdevimab	Casirivimab	Imdevimab	Casirivimab	Imdevimab
1200mg SC L_D + 600mg SC M_D	29.8	24.4	29.3	22.6	28.9	21.3
1200mg IV L_D + 600mg IV M_D	43.6	35.3	43.9	34.5	44.3	33.8

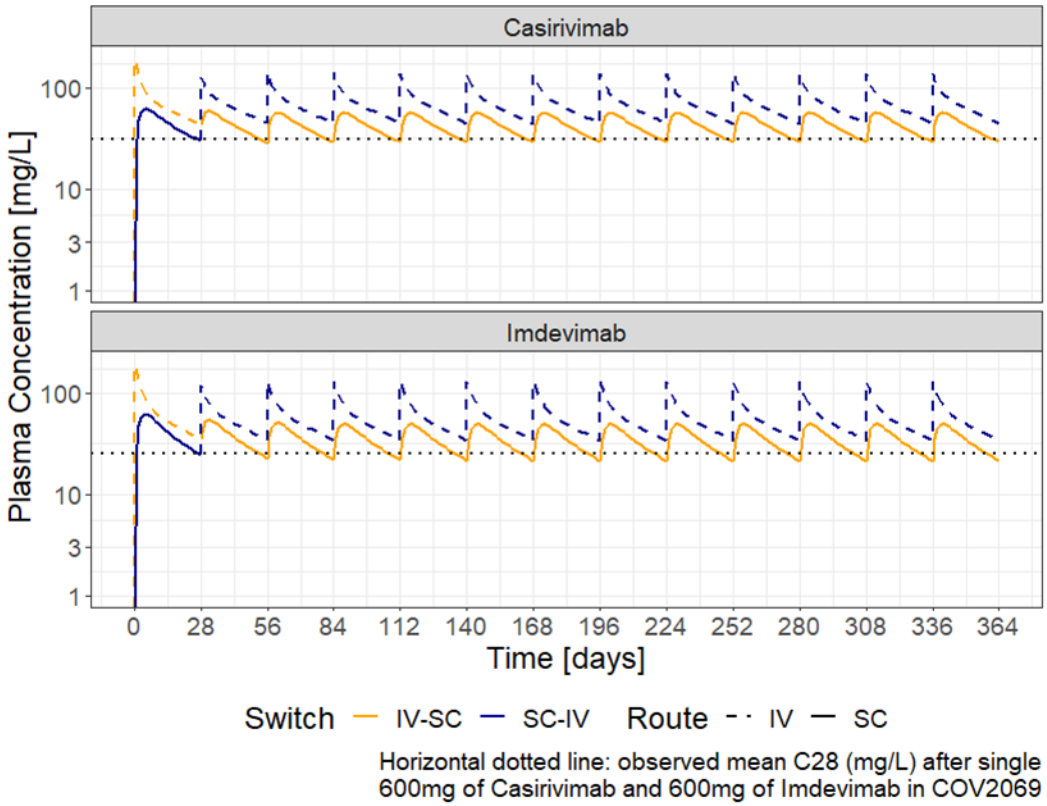
The base population PK models (2-compartment with linear clearance from central compartment) was developed independently for casirivimab and imdevimab, respectively. Absorption rate constant was fixed during model fitting for casirivimab. The base model predicted plasma concentration at D28 were reasonably close to observations and Applicant's simulation.
L_D: loading dose; M_D: maintenance dose

Figure 2: Predicted Mean Serum Concentration for Casirivimab and Imdevimab: a Loading Dose of 600 mg of Casirivimab and 600 mg of Imdevimab Followed by Maintenance Doses of 300 mg of Casirivimab and 300 mg of Imdevimab



As the Applicant proposed allowing switching of the routes of administration at any time during repeat-dosing, the review team conducted additional simulations to reflect these scenarios. The results indicate that the simulated steady state concentration with switching of the routes of administrations did not result in significant changes in overall PK profiles or predicted Ctrough concentrations (Figure 3, Table 18)

Figure 3: Predicted Mean Serum Concentration for Casirivimab and Imdevimab for Switching Dose Regimen (IV-SC and SC-IV): a Loading Dose of 600 mg of Casirivimab and 600 mg of Imdevimab Followed by 12 Maintenance Doses of 300 mg of Casirivimab and 300 mg of Imdevimab



Population PK model predicted serum concentrations of casirivimab and imdevimab following switching of the routes of administrations are shown below in Table 18.

Table 18: Predicted Mean Serum Concentration for Casirivimab and Imdevimab at Day 28, 56, and Steady State for Switching Dose Regimen (IV-SC and SC-IV): a Loading Dose of 600 mg of Casirivimab and 600 mg of Imdevimab Followed by 12 Maintenance Doses of 300 mg of Casirivimab and 300 mg of Imdevimab

Predicted Mean Concentration (mg/L)						
	C_{Day28}		C_{Day56}		$C_{trough,ss}$	
	Casrivimab	Imdevimab	Casrivimab	Imdevimab	Casrivimab	Imdevimab
1200mg SC L_D + 600mg IV M_D	29.8	24.4	44.7	34.2	44.3	33.8
1200mg IV L_D + 600mg SC M_D	43.6	35.3	28.6	22.6	28.9	21.3

The base population PK models (2-compartment with linear clearance from central compartment) was developed independently for casirivimab and imdevimab, respectively. Absorption rate constant was fixed during model fitting for casirivimab. The base model predicted plasma concentration at D28 were reasonably close to observations and Applicant's simulation.
L_D: loading dose; M_D: maintenance dose

Rationale for dosing recommendations

Post exposure prophylaxis

Analysis of data from trial COV-2069 demonstrate an 81% risk reduction in COVID-19 in the group receiving single dose of 600 mg of casirivimab and 600 mg imdevimab administered together subcutaneously compared to placebo, in the 29 day post-dose assessment period. The Applicant proposed both subcutaneous and intravenous routes of administration for the post-exposure prophylaxis indication. Intravenous dosing of casirivimab and imdevimab was not evaluated in trial COV-2069. However, systemic concentrations following intravenous administration are higher relative to the subcutaneous route of administration over the first 28 days (refer to Table 15, Table 16). In addition, the clinical benefit of intravenous administration of REGEN-COV for the treatment of mild and moderate COVID-19 has been demonstrated in COV-2067. The safety of intravenous administration of 600 mg of casirivimab and 600 mg of imdevimab has also been characterized for the treatment of mild and moderate COVID-19 in COV-2067; and intravenous administration is acceptable for post-exposure prophylaxis of COVID-19. Therefore, we accept Applicant's proposal for single dose of 600 mg of casirivimab and 600 mg imdevimab using either subcutaneous administration or intravenous administration.

Repeat dosing prophylaxis

The efficacy of the proposed dosing regimen for repeat dose prophylaxis, 600 mg of casirivimab and 600 mg of imdevimab administered together followed by

monthly 300 mg casirivimab and 300 mg imdevimab, has not been evaluated in clinical trials, but is supported by the totality of evidence as follows.

Following the administration of the proposed dosing regimen, overall exposures after the second dose onwards are expected to be similar to those observed following the administration of the loading dose (Figure 2). Ctrough values after the second dose onwards are expected to be similar to those observed on Day 28 following the administration of the loading dose (Table 17). Since the efficacy of the loading dose of carisivimab and imdevimab for post-exposure prophylaxis has been demonstrated in Trial 2069, maintaining similar exposures following multiple dose administration is a reasonable approach to ensure prophylactic effects for individuals in whom repeat dosing is determined to be appropriate. In addition, the review team has concluded that the observed Day 28 concentrations following the administration of a single dose of 600 mg casirivimab and 600 mg of imdevimab are expected to have adequate antiviral activities *in vivo* supporting the treatment indication.

The safety of the proposed dosing regimen is supported by trial COV-2093 (See XI. Clinical Safety). The maintenance portion of the proposed dosing regimen (i.e., the second dose onwards) is lower than the dose evaluated in trial COV-2093 and no significant accumulation in casirivimab or imdevimab is expected following the administration of the proposed dosing regimen (Figure 2).

Rationale for dosing recommendations in pediatric patients and other specific populations

- Pediatric patients: The safety and effectiveness of casirivimab and imdevimab are being assessed in pediatric and adolescent patients in an ongoing clinical trial. Serum exposures of casirivimab and imdevimab in pediatric patients 12 years of age and older and weighing at least 40 kg is not available yet. The recommended dosing regimen is expected to result in comparable serum exposures of casirivimab and imdevimab in pediatric patients 12 years of age and older and weighing at least 40 kg as those observed in adults since adults with similar body weight have been included in trials COV 2067, COV-2069, and COV-2093.
- Patients with renal impairment: Casirivimab and imdevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of casirivimab and imdevimab.
- Patients with hepatic impairment: The effect of hepatic impairment on PK of casirivimab and imdevimab is unknown.
- Other specific populations: The effect of other covariates (e.g., age, sex, race, body weight, disease severity) on PK of casirivimab and imdevimab is unknown.

Drug-drug interactions

Casirivimab and imdevimab 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.

XII. Nonclinical Data to Support Safety

- Casirivimab and imdevimab were evaluated either alone or administered together in a GLP 4-week repeat-dose toxicology study in cynomolgus monkeys with an 8-week recovery using both intravenous and subcutaneous dosing.
    - No adverse, drug-related findings were observed in this study up to the highest doses tested (150 mg/kg/mAb) by either the intravenous or subcutaneous routes. The safety factor at the NOAEL of 150 mg/kg/mAb, is approximately 15 relative to the proposed human dose of 600 mg/mAb in a 60-kg adult.
    - Minor, non-adverse liver toxicity (~2- to 3-fold increases in AST, ALT and LDH) were observed at the high dose on Day 2 and 7, but appeared to recover by Day 27. No histopathology correlates were observed.
- GLP tissue cross-reactivity studies were also conducted in both normal adult and select fetal human and cynomolgus monkey tissues. No binding of clinical concern was observed with either casirivimab or imdevimab in either species in these studies.

XIII. Nonclinical Data to Support Efficacy

Casirivimab and imdevimab were assessed in non-clinical studies of mechanism of action, epitope mapping, binding, neutralization, effector function, resistance, and antibody-dependent enhancement (ADE) of infection. Activity was assessed in treatment and prevention studies in rhesus macaque and hamster models of SARS-CoV-2 infection.

- Casirivimab and imdevimab bound recombinant trimerized SARS-CoV-2 spike protein with K_D = 45.8 pM and 46.7 pM, respectively. In competitive binding experiments using surface plasmon resonance (SPR) technology, imdevimab bound recombinant receptor binding domain (RBD) protein that was pre-saturated with casirivimab, and casirivimab bound RBD protein that was pre-saturated with imdevimab.

- Casirivimab, imdevimab and the casirivimab + imdevimab combination mediated concentration-dependent blocking of 100 pM RBD binding to ACE2 with IC_{50} values of 56.4 pM, 165 pM and 81.8 pM, respectively.

- Antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) were assessed using Jurkat target cells expressing SARS-CoV-2 spike protein. Casirivimab, imdevimab and the casirivimab + imdevimab combination mediated concentration-dependent ADCC with human natural killer (NK) effector cells, with EC_{50} values in the low nanomolar to picomolar range. Casirivimab, imdevimab and the casirivimab + imdevimab combination mediated concentration-dependent ADCP with human macrophages, with EC_{50} values of 6.54 pM, 10.4 pM and 9.44 pM, respectively.

- Casirivimab, imdevimab and the casirivimab + imdevimab combination did not mediate complement-dependent cytotoxicity in cell-based assays.

- Casirivimab, imdevimab and the casirivimab + imdevimab combination mediated concentration-dependent neutralization of SARS-CoV-2-S pseudotyped VSV-ΔG, VSV-SARS-CoV-2-S virus, and SARS-CoV-2 entry into Vero or Vero E6 cells, with EC_{50} and EC_{90} values in the picomolar range. Against SARS-CoV-2 (USA-WA1/2020 isolate), the neutralization EC_{50} values of casirivimab, imdevimab and the casirivimab + imdevimab combination were 37.4 pM, 42.1 pM and 31.0 pM, respectively, and the EC_{90} values were 178 pM, 430 pM and 173 pM, respectively.

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

- In neutralization assays using VSV virus-like particles (VLP) pseudotyped with spike protein variants identified in circulating SARS-CoV-2, variants with reduced susceptibility to casirivimab alone included those with E406D (51-fold), V445T (107-fold), E484Q (19-fold), G485D (5-fold), G476S (5-fold), F486L (61-fold), F486S (>715-fold), Q493E (446-fold), Q493R (70-fold), and S494P (5-fold) substitutions, and variants with reduced susceptibility to imdevimab alone included those with P337L (5-fold), N439K (463-fold), N439V (4-fold), N440K (28-fold), K444L (153-fold), K444M (1,577-fold), G446V (135-fold), N450D (9-fold), Q493R (5-fold), Q498H (17-fold), P499S (206-fold) substitutions. The G476D substitution had an impact (4-fold) on casirivimab and imdevimab together.

- Casirivimab and imdevimab individually and together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions found in the B.1.1.7 lineage (Alpha; UK origin) and against pseudotyped VLP expressing only N501Y found in B.1.1.7 and other circulating lineages. Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing all spike protein substitutions, or individual substitutions K417N, E484K or N501Y, found in the B.1.1351 lineage (Beta; South Africa origin), and all spike protein substitutions or key substitutions K417T, E484K or N501Y, found in the P.1 lineage (Gamma; Brazil origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing K417N or E484K, as indicated above. The E484K substitution is also found in the B.1.526 lineage (Iota; USA [New York] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against the L452R substitution found in the B.1.427/B.1.429 lineages (Epsilon; USA [California] origin). Casirivimab and imdevimab, individually and together, retained neutralization activity against pseudotyped VLP expressing L452R+T478K substitutions found in the B.1.617.2 lineage (Delta; India origin). Casirivimab and imdevimab together retained neutralization activity against pseudotyped VLP expressing L452R+E484Q substitutions, found in the B.1.617.1/B.1.617.3 lineages (Kappa/no designation; India origin), although casirivimab alone, but not imdevimab, had reduced activity against pseudotyped VLP expressing E484Q, as indicated above.

- In a plaque reduction assay, casirivimab and imdevimab together retained activity against authentic SARS-CoV-2 variants of B.1.1.7 (Alpha), B.1.351 (Beta) and B.1.617.1 (Kappa) lineages, although casirivimab alone, but not imdevimab, had reduced activity against B.1.351 (5-fold) and B.1.617.1 (6-fold) variants. Note that confirmatory sequencing of each of the tested isolates has not yet been completed.

- The potential of casirivimab and of imdevimab to mediate viral entry was assessed in immune cell lines co-incubated with VSV-ΔG expressing an mNeon fluorescent reporter pseudotyped with SARS-CoV-2 spike protein at concentrations of mAb(s) down to approximately 20-fold below the respective neutralization EC_{50} values. The casirivimab + imdevimab combination and imdevimab alone, but not casirivimab alone, mediated entry of pseudoparticles into $FcγR2^+$ Raji and $FcγR1^+/FcγR2^+$ THP1 cells (maximum infection in total cells of 1.34% and 0.24%, respectively, for imdevimab; 0.69% and 0.06%, respectively for the casirivimab + imdevimab combination), but not any other cell lines tested (IM9, K562, Ramos and U937 cells).

- Treatment and prevention studies of the casirivimab + imdevimab combination were conducted in rhesus macaque and hamster models of SARS-CoV-2 infection (Table 19).

Table 19: Relevant Studies of the Product in Animal Models of Disease

Study Number	IND, BLA, or Literature Reference	Type of Study[14]	Species/ Number of Animals Per Group	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Route(s) of Administration; Duration	Study Status
N/A	Baum et al., 2020	Prophylaxis Non-GLP	Rhesus macaques (n=6 in each group)	Animals treated with casirivimab + imdevimab together or placebo control solution, 3 days prior to intranasal and intratracheal inoculation with $1x10^5$ PFU of SARS-CoV-2 (USA-WA1/2020 isolate).	Casirivimab + imdevimab together: 50 mg/kg, dosed intravenously. 5-day study.	Complete
N/A	Baum et al., 2020	Treatment and prophylaxis Non-GLP	Rhesus macaques (n=4 in each group)	Animals treated with casirivimab + imdevimab together or placebo control one day after (treatment), or 3 days before (prophylaxis) intranasal and intratracheal inoculation with $1x10^6$ PFU of SARS-CoV-2 (USA-WA1/2020 isolate).	Casirivimab + imdevimab together: 25 mg/kg or 150 mg/kg (treatment), and 0.3 mg/kg or 50 mg/kg (prophylaxis); dosed intravenously. 7-day study.	Complete
N/A	Baum et al., 2020	Treatment and prophylaxis Non-GLP	Syrian golden hamster (aged 6-8 weeks, n=5 per group)	Animals treated with casirivimab + imdevimab together, or isotype controls, one day after (treatment) or 2 days before (prophylaxis) intranasal inoculation with 2.3×10^4 PFU SARS-CoV-2 (USA-WA1/2020 isolate).	Casirivimab + imdevimab together: 0.5, 5 or 50 mg/kg dosed intraperitoneally. 7-day study.	Complete
N/A		Prophylaxis Non-GLP	Syrian golden hamster (aged 6 weeks, n=7 per mAb group; n=5 per control group)	Animals treated with casirivimab + imdevimab together or control (0.1% polysorbate 80 in saline), 2 days prior to infection with 1×10^4 PFU SARS-CoV-2 (USA-WA1/2020 isolate). Mock infected control group included in study.	Casirivimab + imdevimab together: 0.0005, 0.005, 0.05, 0.5 or 5 mg/kg. 7-day study.	Complete

PFU=plaque-forming units.

The rhesus macaque model is widely used to assess activity of SARS-CoV-2 therapeutics and vaccines and displays a transient and mild course of disease (Chandrashekar et al., 2020). The Applicant conducted two studies in rhesus macaques: the first assessed the impact on SARS-CoV-2 infection of prophylaxis with casirivimab + imdevimab administered together, and the second assessed

[14] May include pharmacokinetic, exposure-response, treatment, post-exposure prophylaxis, pre-exposure prophylaxis, etc.; discuss further as appropriate based on bullet points below. Specify whether GLP.

treatment and prophylaxis with a higher virus inoculum. In the first study, viral genomic RNA and sub-genomic RNA were measured in nasopharyngeal swabs and bronchioalveolar fluid (BALF); in the second study, nasopharyngeal and oral swabs were assessed. Lung histopathology was assessed at the end of both studies.

In the treatment setting, animals treated with casirivimab + imdevimab 25 mg/kg or 150 mg/kg displayed accelerated viral clearance compared to placebo-treated animals in nasopharyngeal and oral swabs samples, including both genomic and sub-genomic RNA. All four placebo monkeys showed evidence of lung injury characterized in three monkeys by interstitial pneumonia, whereas in the treatment groups, 2 of 4 low dose (25 mg/kg) and 2 of 4 high dose (150 mg/kg) treated animals showed evidence of interstitial pneumonia.

In the first prevention study in rhesus macaques, administration of 50 mg/kg casirivimab and imdevimab together prior to challenge with SARS-CoV-2 demonstrated reduction in genomic and sub-genomic viral RNA via nasal swabs and bronchioalveolar lavage fluid as well as a reduction in lung inflammation.

In the second prevention study in rhesus macaques, 50 mg/kg of casirivimab + imdevimab administered 3 days prior to virus challenge demonstrated significant reduction in genomic RNA and sub-genomic RNA via nasopharyngeal and oral swabs compared with animals receiving placebo. The prophylactic effect was greatly diminished with the 0.3 mg/kg dose. The incidence of lung inflammation was reduced in animals prophylactically treated with 50 mg/kg of the casirivimab + imdevimab combination compared to placebo.

The Syrian golden hamster model has a severe course of SARS-CoV-2 infection, with animals demonstrating readily observable clinical disease, including rapid weight loss accompanied by high viral load in lungs, and severe lung pathology (Chan et al., 2020; Imai et al., 2020). The Applicant conducted two studies in the hamster model: the first assessed the impact on SARS-CoV-2 infection of treatment or prophylaxis with casirivimab and imdevimab administered together, and the second assessed potential for antibody-dependent enhancement of infection in a prophylaxis setting.

In the treatment setting, hamsters dosed with 50 mg/kg or 5 mg/kg of casirivimab + imdevimab together 1-day post viral challenge showed protection from weight loss. A dose-dependent effect of casirivimab + imdevimab treatment on viral RNA levels in oral swabs and lungs was not clear in this study, although in general there was an impact on genomic and sub-genomic RNA levels.

In the first prevention study in hamsters, administration of 0.5 mg/kg, 5 mg/kg, or 50 mg/kg casirivimab + imdevimab together prior to challenge with SARS-CoV-2 protected against weight loss, and reduced percentage of lung area with pathology typical of pneumonia and severity of lung inflammation, indicative of

reduced morbidity in this model. Overall, there was an impact of casirivimab + imdevimab together on genomic and sub-genomic RNA levels in oral swabs and lungs, which was not clearly dose-dependent.

In the second prevention study in hamsters studying antibody-dependent enhancement of infection, administration of a range of casirivimab + imdevimab doses from 0.0005 mg/kg to 5 mg/kg showed a dose-dependent effect on weight loss and on severity of lung inflammation, with the greatest effects at the 5 mg/kg dose. Animals treated with 5 mg/kg also showed decreased levels of viral RNA in the lungs compared with the control (infected) group. In general, there were no clear differences in lung viral load for lower doses compared with control animals. Overall, there was no evidence of increased weight loss, lung pathology or viral load at any dose of casirivimab + imdevimab compared with control, indicating a lack of antibody-dependent enhancement of infection. It should be noted, however, that based on studies conducted by the Applicant, human IgG1 binds hamster Fcγ receptors with lower affinity than human Fcγ receptors, so this study may not be fully relevant.

XIV. Supply Information

- Quantity of drug product needed for one treatment course per individual for proposed EUA use (adults and pediatric persons 12 years of age and older weighing at least 40 kg): 1200 mg (600 mg of casirivimab and 600 mg of imdevimab) administered as intravenous infusion or subcutaneous injection.

- In correspondence dated July 22, 2021, the Applicant stated that 1.25 million doses of coformulated product were available by June 30, 2021. The dose pack bags are not in the Applicant's current production plans, and there are approximately (b) (4) dose pack bags in inventory available for distribution from the U.S. Strategic National Stockpile as of July 21, 2021.

XV. Chemistry, Manufacturing, and Controls Information

Casirivimab (REGN10933) and imdevimab (REGN10987) are recombinant human immunoglobulin G-1 (IgG1) monoclonal antibodies produced in Chinese Hamster Ovary (CHO) cells that target the receptor binding domain (RBD) of respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) protein. Casirivimab and imdevimab are covalent heterotetramers consisting of 2 heavy chains and 2 light chains. The heavy chains contain an N-linked glycan site at asparagine 300 (Asn300). The mechanism of action is to inhibit the interaction between S protein and angiotensin-converting enzyme 2 (ACE2) receptors on host cells, thereby blocking viral entry into cells. Casirivimab and imdevimab also elicit antibody-dependent cellular cytotoxicity (ADCC).

Casirivimab and imdevimab are supplied in individual vials or are co-formulated in the same vial. For individual vials, each antibody is supplied in a single-dose

glass vial, as a liquid solution for injection. The casirivimab and imdevimab formulations are the same: 120 mg/mL of antibody, (b) (4) histidine, 8% (w/v) sucrose, and 0.1% (w/v) polysorbate 80, pH 6.0. Two strengths are available for each antibody: 300 mg in 2.5 mL, and 1332 mg in 11.1 mL. For co-formulated solution, casirivimab and imdevimab are mixed in a 1:1 ratio in a single dose vial. The co-formulated solution formulation is: 120 mg/mL of antibody (60 mg/60 mg per mL of each antibody), (b) (4) histidine, 8% (w/v) sucrose, and 0.1% (w/v) polysorbate 80, pH 6.0. IND 148069 was referenced for this EUA and contains the supporting CMC information.

The manufacturing processes are adequately controlled to support consistent production of materials for EUA that are pure and potent. The overall control strategy for drug substance (DS) and drug product (DP) is comprehensive for control of raw materials, performance, and product quality attributes. DS and DP of casirivimab and imdevimab are separately manufactured. The DS is manufactured at Regeneron Rensselaer (Rensselaer, NY) and Regeneron Ireland DAC (Limerick, Ireland). The DP is manufactured at (b) (4) and (b) (4). DS is manufactured at either (b) (4) L or (b) (4) L bioreactor scale. The only major difference is the bioreactor scale in the manufacturing processes as detailed in IND 148069. Analytical comparability data, including results from in-process tests, batch release, characterization, and stress stability performed on pre- and post-change lots support that the DS and DP materials produced at (b) (4) L scale are comparable to materials produced at (b) (4) L scale.

The individual DS manufacturing process consists of (b) (4) The DP manufacturing process consists of (b) (4) Equipment and components are sterilized by the supplier and provided ready to use; sterility assurance during the aseptic process has been demonstrated by media fill simulations. The DP vials are stored at 5ºC. Details of the manufacturing processes are provided in IND 148069.

(b) (4). Two-tiered cell banking system of

Master cell banks (MCBs) and working cell banks (WCBs) are in place to maintain consistent source of each antibody product. The cell lines are tested in accordance with ICH Q5A to demonstrate assurance of safety of the MCB and WCB for production use. The DS processes are sufficiently qualified for inactivation or removal of adventitious agents. Viral safety controls, including raw material control, unprocessed bulk testing, and viral clearance studies, are acceptable to support the viral safety of the product for use under EUA.

Detailed characterization data, including primary, secondary, and high order structure, established and/or potential mechanisms of actions, product- and process-related species are provided in IND 148069. The DS and DP specifications, analytical methods, and batch analysis data are acceptable to support the EUA. Comparability data provided, including in-process testing data, release data, characterization data, and stress condition stability data, support the comparability between materials to be distributed under EUA and materials used in clinical studies to support EUA.

The requested expiration dating period of (b) (4) at 5ºC for individual antibodies is supported by a risk assessment based on the available drug product stability data, including up to (b) (4) at the long-term storage condition of 5ºC and (b) (4) at the accelerated storage condition of 25ºC/60% RH. Results from a (b) (4) stability study at the stress condition of 45ºC further support expiry dating. The requested expiration dating period of (b) (4) at 5ºC for coformulated drug product is supported by a risk assessment based on the available drug product stability data, including up to (b) (4) research stability data at 5ºC, the comparability assessment, and the experience from other coformulated product. The stability protocols are adequate to detect potential changes in critical quality attributes during storage. The Sponsor committed to update IND 148069 with stability data from ongoing studies to further support the proposed (b) (4) shelf life, and to notify the Agency in the event that Out of Specification (OOS) results occur.

XVI. Manufacturing Site Inspections

The following manufacturing and testing facilities are acceptable for the purpose of the EUA. Additional DS and DP manufacturing sites may be added to the EUA. These sites will be evaluated at the time of submission.

Table 20: Manufacturing Sites

Manufact-uring Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant	Inspection Dates	GMP Status (if known)
Regeneron Pharmaceuticals, Inc. (FEI 1000514603)	DS manufacture, release, and stability testing	Rensselaer, NY	IND-148069	Regeneron Pharmaceuticals, Inc.	October 2019	Acceptable
Regeneron Ireland DAC (FEI 3011684330)	FDS manufacture, release, and stability testing	Limerick, Ireland	IND-148069	Regeneron Pharmaceuticals, Inc.	May 2021	Acceptable
(b) (4)	DP manufacturing, inspection, and bulk packaging of vials and product testing	(b) (4)	IND-148069	Regeneron Pharmaceuticals, Inc.	(b) (4)	Acceptable
	DP manufacturing, labeling, packaging, and product testing		IND-148069	Regeneron Pharmaceuticals, Inc.		Acceptable
	(b) (4)		IND-148069	Regeneron Pharmaceuticals, Inc.		Acceptable

XVII. Clinical Trial Site Inspections

Clinical site inspections were not conducted for this EUA amendment.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

Nonclinical site inspections were not conducted for this EUA amendment.

XIX. Recommendations From Treatment Guidelines and Other Sources

At this time, there are no authorized or approved therapies for post-exposure prophylaxis of COVID-19. The Centers for Disease Control, Infectious Diseases Society of America, and the NIH COVID-19 Treatment Guidelines do not suggest a specific therapy for post-exposure prophylaxis of COVID-19.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Recommendation for Authorization for Post-exposure Prophylaxis

Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that bind to different but overlapping epitopes in the receptor binding domain of the spike protein of SARS-CoV-2. Casirivimab and imdevimab have demonstrated activity in cell culture and animal models against SARS-CoV-2. These antibodies have been evaluated in phase 1, 2 and 3 clinical trials for both treatment and post-exposure prophylaxis indications.

Based on review of topline results from phase 3 trial COV-2069 which demonstrate the efficacy of 600 mg of casirivimab and 600 mg of imdevimab for post-exposure prophylaxis of COVID-19, it is reasonable to believe that 600 mg of casirivimab and 600 mg of imdevimab may be effective for post-exposure prophylaxis of COVID-19 in individuals how are who are at high risk for progression to severe COVID-19 including hospitalization or death, **and** are not fully vaccinated[15] **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications[16]), **and** have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC[17] **or** who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons). The known and potential benefits of casirivimab and imdevimab, administered together, outweigh the known and potential risks for the proposed authorized use.

The primary data supporting this authorization are from COV-2069, a randomized, double-blind, placebo-controlled trial conducted in individuals who were household contacts of SARS-CoV-2 infected patients. Asymptomatic household contacts were randomized 1:1 to a single dose of 600 mg of casirivimab and 600 mg of imdevimab or placebo administered subcutaneously. The primary analysis population consisted of 1505 subjects who were SARS-CoV-2 RT-qPCR negative and seronegative at baseline. The primary efficacy endpoint was the proportion of subjects who developed symptomatic RT qPCR-

[15] Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated

[16] See this website for more details: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

[17] Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

confirmed SARS-CoV-2 infection through Day 29. An 81% risk reduction in symptomatic SARS-CoV-2 infection was observed with REGEN-COV treatment (1%) compared to placebo (8%) which was statistically significant. In addition, there was a 66% risk reduction in any RT-qPCR confirmed SARS-CoV-2 infection (symptomatic or asymptomatic) with REGEN-COV treatment (5%) compared to placebo (14%) which was also statistically significant. In a post-hoc analysis in the subgroup that met the criteria for high risk for progression to severe COVID-19, as defined in the EUA Fact Sheet, there was a 76% risk reduction in symptomatic SARS-CoV-2 infection with REGEN-COV (2%) compared to placebo (7%) which was statistically significant. In Cohort B, asymptomatic subjects with a positive SARS-CoV-2 RT-qPCR test result at baseline were enrolled and randomized 1:1 to REGEN-COV or placebo. In post-hoc analysis of the overall combined Cohort A and Cohort B (regardless of serology status at baseline), a nominally significant 62% risk reduction in COVID-19 with REGEN-COV treatment versus placebo was observed. Separately, we note the efficacy of this same dose, 600 mg of casirivimab and 600 mg of imdevimab, in trial COV-2067 which supported EUA issuance for the treatment indication in mild to moderate COVID-19 in non-hospitalized patients at high risk of progression to severe COVID-19.

The safety profile in COV-2069 was generally similar to the known safety profile with intravenous administration of casirivimab and imdevimab, with the exception of an additional concern for injection site reactions that is specific to the subcutaneous route of administration. Local erythema, pruritus, and ecchymosis were the most commonly occurring injection site reactions; and all injection site reactions were mild or moderate in severity. There were no cases of anaphylaxis or anaphylactic reactions. Hypersensitivity reactions were observed; all hypersensitivity reaction events were mild to moderate in severity. Most events did not require medical management, however, a few cases required administration of antihistamines and analgesic medications. Based on all the currently available safety data, a post-dose observation period of at least one hour is recommended after dosing for post-exposure prophylaxis. REGEN-COV should be administered in settings in which health care providers would have immediate access to medications to treat a severe infusion or hypersensitivity reaction such as anaphylaxis and the ability to activate the emergency medical system, as necessary.

While subcutaneous administration was evaluated COV-2069, the pharmacokinetic profiles with subcutaneous and intravenous administration of 600 mg of casirivimab and 600 mg of imdevimab, as well as the clinical safety data for intravenous administration of this dose in the treatment trial COV-2067 (which supported the EUA issuance for the treatment indication) support intravenous dosing of this single dose for post-exposure prophylaxis.

Certain individuals with ongoing exposure to SARS-CoV-2 may benefit from repeat dosing. Repeat doses of 300 mg of casirivimab and 300 mg of imdevimab

administered every 4 weeks yield antibody exposures similar to those achieved with the 600 mg of casirivimab and 600 mg of imdevimab. The safety profile with repeat dosing every 4 weeks for 24 weeks in trial COV-2093 was similar to the safety profile observed with single dose administration in COV-2069. Injection site reactions of mild to moderate severity were the common adverse events with repeat dosing. Based on these clinical pharmacology and safety data, repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab, administered together, will be authorized for individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-COV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination. For such individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure. The use of REGEN-COV will be contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis.

The SARS-CoV-2 vaccines that are authorized under EUA are the primary form of prevention; and post-exposure prophylaxis with casirivimab and imdevimab is not a substitute for vaccination against COVID-19, as communicated in the Limitations of Authorized Use statement in the Healthcare Provider Fact Sheet.

Additionally, the scope of the intended population for post-exposure prophylaxis is limited to individuals at high risk for progression to COVID-19 who are not fully vaccinated as defined by the CDC, or those who are not expected to mount an adequate response to complete SARS-CoV-2 vaccination. The CDC considers individuals to be fully vaccinated two weeks after their 2nd vaccine dose in a 2-dose series (e.g., the Pfizer or Moderna vaccines); or two weeks after a single-dose vaccine (such as the Johnson & Johnson's Janssen vaccine). Certain immunosuppressive conditions and immunosuppressive medications are reported to reduce antibody response to COVID-19 vaccination. The indication language in the Fact Sheet includes examples of these conditions and cites the CDC's website as a resource to guide the treating physicians who are considering the use of REGEN-COV prophylaxis in an individual expected to develop inadequate response to complete SARS-CoV-2 vaccination. To ensure correct use under EUA, the Limitations of Authorized Use specifies that REGEN-COV is not authorized for pre-exposure prophylaxis for prevention of COVID-19.

In addition, the scope of authorization specifies use based on exposure to an individual infected with SARS-CoV-2 or at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes,

prisons). Although trial COV-2069 evaluated post-exposure prophylaxis of REGEN-COV in the context of households with SARS-CoV-2 infected cases, the benefit observed in this trial can be applied to other settings where effective post-exposure prophylaxis could offer benefit. Congregate settings such as nursing homes, prisons are examples of institutional settings where individuals may face a high risk of exposure to a patient infected with SARS-CoV-2. The Fact Sheet does not outline every specific setting where post-exposure prophylaxis may be useful; instead, the Fact Sheet provides reference to CDC's website to allow healthcare providers to determine the risk exposure based on CDC's criteria for defining close contact with an individual infected with SARS-CoV-2, and by including the CDC website as a source of reference.

Trial COV-2069 was initiated prior to SARS-CoV-2 vaccine authorizations and did not enroll vaccinated individuals; and the effects of casirivimab and imdevimab on potential attenuation of vaccine response are not known at the present time. It is unclear how the administration of casirivimab and imdevimab together for post-exposure prophylaxis in an unvaccinated individual will affect the response to vaccination in the future. The Applicant is currently conducting a clinical trial to evaluate the possible effect of casirivimab and imdevimab on vaccine-induced immune responses.

The currently circulating SARS-CoV-2 variants of concern/variants of interest are likely susceptible to casirivimab and imdevimab administered together based on pseudotyped VLP and authentic virus neutralization data. However, it is not known whether the clinical effectiveness against these variants is the same as observed in the clinical trial described above, which was largely conducted prior to these variants becoming prevalent. Also, there is a potential for variants to arise in the future which have reduced susceptibility to both antibodies in the combination.

In sum, based on the totality of the scientific information available, including the efficacy and safety of 600 mg of casirivimab and 600 mg of imdevimab demonstrated in the phase 3 post-exposure prophylaxis trial COV-2069, it is reasonable to believe that the authorized dose of 600 mg of casirivimab and 600 mg of imdevimab administered together may be effective for the proposed authorized use of post-exposure prophylaxis of COVID-19 and the known and potential benefits outweigh the known and potential risks. In certain individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2 for longer than 4 weeks and who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by subcutaneous injection or intravenous infusion followed by subsequent repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab by subcutaneous injection or intravenous infusion once every 4 weeks for the duration of ongoing exposure. This repeat dosing may be effective for the proposed authorized use of post-exposure prophylaxis and the known and potential benefits outweigh the known

and potential risks. Therefore, the Review Division and the Office of Infectious Diseases conclude that the statutory standards are met and recommend extending the authorization of 600 mg of casirivimab and 600 mg of imdevimab administered together with repeat dosing of 300 mg of casirivimab and 300 mg of imdevimab once every 4 weeks for the duration of ongoing exposure for post-exposure prophylaxis of COVID-19.

Recommendation for declining the Applicant's request to extend the treatment indication (b) (4)

We have determined that the EUA criteria are not met for the Applicant's request (b) (4) Based on the totality of scientific evidence available, including the findings in COV-2069 Cohort B, the data are insufficient to conclude that REGEN-COV may be effective for (b) (4) As such, given the above, we cannot conclude that the known and potential benefits of REGEN-COV for this proposed use outweigh the known and potential risks of the product, and the EUA statutory criteria are not met. We base these determinations on the following:

In the overall population, the treatment differences for REGEN-COV versus placebo did not demonstrate clinical or nominal significance for the endpoint of reduction in the incidence of COVID-19 related hospitalization or death (REGEN-COV 0% [0/155] and placebo 2% [3/156]), which are clinically important endpoints in the context of a treatment indication for an EUA. In the seronegative population, these results were also not significant at the two-sided 0.05 significance level (REGEN-COV 0% [0/100] and placebo 3% [3/104]). While REGEN-COV prevented development of symptomatic infection in asymptomatic PCR-positive subjects, the findings did not translate into prevention of hospitalization or death in comparison to placebo. As such, the outcomes from COV-2069 cohort B are viewed as exploratory and do not meet the EUA statutory criteria to support extending authorization to asymptomatic patients with SARS-CoV-2 infection (note that treatment of asymptomatic SARS-CoV-2 infection is referred to as 'early treatment' in the Applicant's EUA Amendment).

XXI. Considerations for Adverse Event (AE) Monitoring

This product will either be used in clinical trials or in clinical practice under EUA. Investigational product will be used in clinical trials conducted under IND. FDA IND safety reporting regulations will apply.

EUA-labeled product will be made available under the EUA. In the setting of a pandemic where practicing physicians will have many competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system.

The prescribing health care provider and/or the provider's designee will be responsible for mandatory reporting of all medication errors and all serious adverse events considered to be potentially related to casirivimab and/or imdevimab occurring during treatment with casirivimab and/or imdevimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Casivirimab and Imdevimab use for COVID-19 under Emergency Use Authorization (EUA)."

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the Letter of Authorization and the authorized Fact Sheets for Health Care Providers.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

Fact sheets will be available to health care providers and patients through electronic links.

The Applicant has indicated that their plan for electronic distribution of the Fact Sheet for Health Care Providers and Fact Sheet for Patients and Parents and Caregivers is unchanged.

- The URL is www.REGENCOV2.com.

FDA agrees with the plan for implementation for dissemination of the Fact Sheets.

- Fact Sheet for Health Care Providers (See Section XXVI Appendices)
- Dear Healthcare Provider Letter (See Section XXVI Appendices)

XXIV. Outstanding Issues/Data Gaps

Not applicable.

XXV. References

References are included in the relevant sections of this review, where applicable.

XXVI. Appendices

1. Fact Sheet for Health Care Providers
2. Fact Sheet for Patients and Parent/Caregivers
3. Dear Healthcare Provider Letter

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/s/

CHARU J MULLICK
07/30/2021 10:49:04 AM

MARY E SINGER
07/30/2021 10:50:35 AM

DEBRA B BIRNKRANT
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JOHN J FARLEY
07/30/2021 10:58:29 AM

CLINICAL REVIEW
US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTIVIRALS
ADDENDUM

EUA:	000091
Product:	REGN10933 and REGN10987 (casirivimab and imdevimab)
Sponsor:	Regeneron Pharmaceuticals, Inc.
Intended Use:	Post-exposure prophylaxis of coronavirus disease 2019 (COVID-19)
Intended Population:	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, including hospitalization or death, and are: • not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) and o have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Controls and Prevention (CDC) or o who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons)

This addendum is for corrections to the clinical review for EUA 91 eCTD #0048, dated July 30, 2021, which supported the reauthorization of EUA 91 Fact Sheets.

The corrections do not alter the conclusion of the clinical review for EUA 91. The corrections do not alter the information in the approved EUA Healthcare Provider and Patient Fact Sheets.

The correction is as follows:

- On Page 29, VIII. Clinical Efficacy for Study 2069 Cohort B, added "The study did not provide sufficient power to assess this endpoint" at the end of the last paragraph to discuss the results of hospitalization or death in all Cohort B subjects and seronegative population.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIAOJING K QI
08/26/2021 05:03:27 PM

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