

**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) <sup>1</sup>	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. Mobile: (b) (6) Email: <a href="mailto:yunji.kim@regeneron.com">yunji.kim@regeneron.com</a>
Manufacturer	Regeneron Pharmaceuticals, Inc.
Submission Date(s)	October 8, 2020
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OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/Discipline(s)	Charu Mullick, MD – Clinical Reviewer Mary Singer, MD, PhD – Clinical Team Lead David McMillan, PhD – Nonclinical Reviewer Christopher Ellis, PhD – Nonclinical Team Lead Qin Sun, PhD, Clinical Pharmacology Reviewer Su-Young Choi PharmD, PhD – Clinical Pharmacology Team Lead Kellie Reynolds, PharmD – Division Director, DIDP Michael Thomson, PhD – Clinical Virology Reviewer Jules O’Rear, PhD – Clinical Virology Team Lead Karen Qi, PhD – Statistics Reviewer Thamban Valappil, PhD – Statistics Team Lead Dionne Price, PhD – Director, Division of Biometrics IV

<sup>1</sup> 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	November 21, 2020
Proprietary Name	n/a
Established Name/Other names used during development	casirivimab (REGN10933) and imdevimab (REGN10987)
Dosage Forms/Strengths	1200 mg intravenous (IV) casirivimab and 1200 mg IV imdevimab

Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1 monoclonal antibodies (mAbs)
Intended Use or Need for EUA	Mild to moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral test and who are at high risk for progressing to severe COVID-19 and/or hospitalization
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	Please refer to the Letter of Authorization for details

**I. EUA Determination/Declaration**

On February 4, 2020, 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**

The Division of Antivirals, Office of Infectious Diseases, Office of New Drugs, CDER recommends EUA issuance.

The EUA will be issued for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

**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

- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that casirivimab and imdevimab, administered together, may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and when used under such conditions, the known and potential benefits of casirivimab and imdevimab 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 the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. Veklury (remdesivir) is the only drug that is approved by FDA to treat COVID-19 at the time of FDA's review of this EUA request for casirivimab and imdevimab. Remdesivir is a nucleoside ribonucleic acid polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Veklury's FDA-approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) requiring hospitalization, a narrower population than the use authorized for casirivimab and imdevimab under this EUA.

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

#### Proposed Use under EUA:

Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI)  $\geq 35$
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are  $\geq 65$  years of age
- Are  $\geq 55$  years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease
- Are 12 – 17 years of age AND have

- BMI  $\geq$ 85th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](https://www.cdc.gov/growthcharts/clinical_charts.htm), OR
- sickle cell disease, OR
- congenital or acquired heart disease, OR
- neurodevelopmental disorders, for example, cerebral palsy, OR
- a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
- asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

## LIMITATIONS OF AUTHORIZED USE

- Casirivimab and imdevimab are 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.
- Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

### Authorized Dosage under EUA:

#### *Adults and pediatric patients*

The authorized dosage for casirivimab and imdevimab for adults and pediatric patients (12 years of age and older who weigh  $\geq$ 40 kg) is a single intravenous (IV) infusion of 1200 mg of casirivimab and 1200 mg of imdevimab administered together and as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

#### *Pregnant or lactating patients*

No dosage adjustment is recommended. Casirivimab and imdevimab have not been studied in pregnant or 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 dose is based on the regimen that was evaluated in the randomized, double-blinded, placebo-controlled trial R10933-10987-COV-2067 in nonhospitalized patients with symptomatic COVID-19. Analysis of data from trial R10933-10987-COV-2067 showed similar responses with the doses of 1200 mg casirivimab and 1200 mg or 4000 mg casirivimab and 4000 mg imdevimab for virologic outcomes and reduction in hospitalizations and emergency room visits. Therefore, the authorized dose is 1200 mg casirivimab and 1200 mg imdevimab. Casirivimab and imdevimab are administered together as a single IV infusion over a minimum of 60 minutes.

#### **IV. Product Information (Dose Preparation and Administration)**

Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) aqueous solution to be diluted prior to infusion. Imdevimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) aqueous solution to be diluted prior to infusion. IND 148069 was referenced for this EUA and contains the supporting CMC information.

#### *Preparation Instructions*

Casirivimab and imdevimab are each supplied in individual single-dose vials. Casirivimab and imdevimab solutions must be diluted prior to administration.

Casirivimab and imdevimab solution for 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 solution must be discarded, and fresh solution prepared.
  - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.
3. Obtain an IV infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. Withdraw and discard 20 mL of 0.9% Sodium Chloride Injection from the infusion bag prior to adding casirivimab and imdevimab solutions according to Table 1.
4. Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial using two separate syringes and dilute together in the infusion bag containing 0.9% Sodium Chloride Injection, see Table 1. Discard any product remaining in the vial.
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake.** 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 and at room temperature up to 25°C (77°F) for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

**Casirivimab** and **imdevimab** carton and vial labels may instead be labeled **REGN10933** and **REGN10987** respectively.

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

	Antibody Dose	Volume to Withdraw from Vial	Number of Vials Needed <sup>b</sup>	Volume of 0.9% Sodium Chloride to Discard from a 250 mL Infusion Bag	Total Volume for Infusion	Maximum Infusion Rate	Minimum Infusion Time
Casirivimab and Imdevimab 2400 mg Dose <sup>a</sup>	Casirivimab REGN10933 1,200 mg	10 mL	1 vial of 11.1 mL OR 4 vials of 2.5 mL	20 mL	250 mL	250 mL/hr	60 minutes
	Imdevimab REGN10987 1,200 mg	10 mL	1 vial of 11.1 mL OR 4 vials of 2.5 mL				

NOTE: casirivimab = REGN10933; imdevimab = REGN10987

<sup>a</sup> 1,200 mg of Casirivimab and 1,200 mg of Imdevimab are to be administered together as a single intravenous infusion for a combined 2,400 mg dose.

<sup>b</sup> One 11.1 mL vial of one antibody may be prepared with four 2.5 mL vials of the other antibody to create one treatment course.

### *Administration*

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 IV bag.
- Prime the infusion set.

- Administer as an IV infusion via pump or gravity over at least 60 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see **Table 1**).
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush with 0.9% Sodium Chloride Injection.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

### *Storage*

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the individual original carton to protect from light. Do NOT freeze, shake, or expose to direct light.

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

### Background Information on the Condition

There are many types of human coronaviruses including some that commonly cause mild upper-respiratory tract illness. 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 55 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of November 18, 2020, including an estimated 1.3 million deaths. In the US, according to the Center for Disease Control and Prevention (CDC), as of November 18, 2020, approximately 11 million cases of COVID-19 have been reported with 246,232 deaths.

Patients with SARS-CoV-2 infection can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath, or dyspnea, or abnormal chest imaging. Moderate illness is defined as the presence of symptoms including lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation  $\geq 94\%$  on room air; and severe and critical illness defined as worsening pulmonary status requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO. Per the CDC (MMWR March 27, 2020 / 69(12);343-346), between February 12 and March 16, 2020, 4,226

COVID-19 cases were reported in the United States; 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths occurred among adults aged  $\geq 65$  years, with the highest percentage of severe outcomes among persons aged  $\geq 85$  years. These findings are similar to data from China, which indicated  $>80\%$  of deaths occurred among persons aged  $\geq 60$  years (JAMA. 2020;323(13):1239-1242). These preliminary data also demonstrate that severe illness leading to hospitalization, including ICU admission and death, can occur in adults of any age with COVID-19. Per the CDC, 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 COVID-19. Severe illness is defined as hospitalization, admission to the ICU, mechanical ventilation or death (<https://www.cdc.gov/coronavirus/2019-ncov>).

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 (Göttinger et al., 2020).

#### Therapeutic Alternatives for the Disease

There is an approved drug and other EUAs authorized for other COVID-19 treatments. An EUA was authorized for the monoclonal antibody, bamlanivimab, on November 9, 2020 for the treatment of mild-to-moderate 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 progressing to severe COVID-19 and/or hospitalization. An EUA was authorized for baricitinib, in combination with remdesivir, on November 19, 2020 for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. VEKLURY (remdesivir) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor approved for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. This medication was initially authorized for emergency use on May 1, 2020, and ultimately was approved for the treatment of COVID-19 patients requiring hospitalization on October 22, 2020 under NDA 214787.

Additional information on COVID-19 treatments can be found at <https://www.cdc.gov/coronavirus/2019-ncov/index.html>

#### **VI. Related Regulatory Submission(s)**

As of November 9, 2020 more than 2100 clinical trial participants have received an IV infusion of casirivimab and imdevimab, administered together, at doses of 2400 mg IV (1200 mg of each mAb) or 8000 mg IV (4000 mg of each mAb).

Over 1200 participants have received casirivimab and imdevimab subcutaneously (SC) at a dose of (b) (4) ((b) (4) of each mAb) single dose or once every four weeks for up to (b) (4).

- Related INDs

The ongoing clinical trials under IND 148069 and the drug dosages for each trial are summarized as below:

- IND 148069 - casirivimab and imdevimab, administered together

- R10933-10987-COV-2067: Phase 1/2/3, randomized, double-blind, placebo-controlled trial in ambulatory adults with COVID-19 illness, including asymptomatic patients with SARS-CoV-2 infection. This trial includes a potential treatment arm for evaluation of REGN10989, however, this treatment arm is not open to enrollment.

- Dose, duration, and route: casirivimab and imdevimab 2400 mg (1200 mg of each mAb), 8000 mg (4000 mg of each mAb); IV single dose
- Sponsor: Regeneron

- R10933-10987-COV-2066: Phase 1/2/3, randomized, double-blind, placebo-controlled trial in hospitalized adults with COVID-19. This trial includes a potential treatment arm for evaluation of REGN10989, however, this treatment arm is not open to enrollment.

- Dose, duration, and route: casirivimab and imdevimab 2400 mg (1200 mg of each mAb), 8000 mg (4000 mg of each mAb); IV single dose
- Sponsor: Regeneron

- R10933-10987-COV-2069: Phase 3, randomized, double-blind, placebo-controlled prophylaxis trial in household contacts of individuals infected with SARS-CoV-2.

- Dose, duration, and route: casirivimab and imdevimab (b) (4) ((b) (4) of each mAb) SC single dose
- Sponsor: Regeneron

- R10933-10987-COV-2093: Phase 1, randomized, double-blind, placebo-controlled trial assessing the safety and tolerability of multiple subcutaneous doses in adult healthy volunteers.

- Dose, duration, and route: casirivimab and imdevimab (b) (4) ((b) (4) of each mAb) SC every 4 weeks for up to (b) (4)

- Related Master Files (Product Quality reviewer to provide this information)

- Master File Numbers
  - Briefly describe the Master File contents: No Drug Master Files were cross-referenced in this EUA submission
  - Master File holder: Not applicable

## **VII. Summary of Clinical Data**

See Table 2 for details regarding the clinical trials.



				exposure to individuals with SARS-CoV-2 infection	casirivimab and (b) (4) of imdevimab)	
					1-month efficacy assessment period; 7-month follow-up after the end of the efficacy assessment period	
R10933-10987-COV-2093	148069	Safety, PK	N=940 Adult healthy volunteers	Phase 1, randomized, double-blind, placebo-controlled study in adult healthy volunteers, designed to assess the safety and tolerability of multiple subcutaneous doses of REGN10933+REGN10987	(b) (4) SC casirivimab and imdevimab (b) (4) mg of casirivimab and (b) (4) of imdevimab) every 4 weeks for 6 doses  (b) (4) treatment period (or shorter if participant develops symptomatic SARS-CoV-2 infection); (b) (4) follow-up period	Ongoing Enrollment N = (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(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. Multiple investigational arms - azithromycin, convalescent plasma, aspirin, tocilizumab, and low-dose dexamethasone (in children only)	<ul style="list-style-type: none"> <li>8000 mg IV single dose casirivimab and imdevimab (4000 mg of casirivimab and 4000 mg of imdevimab)</li> </ul>	Ongoing

Sources: Adapted from Applicant's submission to EUA 91 dated November 9, 2020 entitled 'EUA 000091 Response to IR', submission to IND 148069 dated October 15, 2020 entitled 'Periodic Development Update'; and the RECOVERY website <https://www.recoverytrial.net/> accessed on November 16, 2020  
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.  
\*not initiated secondary to feasibility issues

## VIII. Clinical Efficacy

### Trial R10933-10987-COV-2067

The main source of clinical efficacy data to support this EUA request was from analysis of phase 1 and 2 data from an ongoing trial R10933-10987-COV-2067 (hereafter referred to as COV-2067) (NCT04425629).

COV-2067 is a phase 1/2/3, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of casirivimab and imdevimab 2400 mg IV or casirivimab and imdevimab 8000 mg or placebo in outpatients (non-hospitalized) with SARS-CoV-2 infection. The trial was originally designed to enroll only symptomatic outpatients. The protocol was modified to include a separate cohort of asymptomatic adults with positive SARS-CoV-2 RT-PCR test. Note that data from the symptomatic cohort were submitted in support of this EUA.

The trial population consisted of eligible adults with laboratory-confirmed SARS-CoV-2 infection, and who were not hospitalized. Eligible participants were randomized 1:1:1 to receiving a single dose of placebo or casirivimab and imdevimab, as follows:

- 2400 mg casirivimab (1200 mg) and imdevimab (1200 mg) (N=266)
- 8000 mg casirivimab (4000 mg) and imdevimab (4000 mg) (N=267)
- Placebo (N=266)

Inclusion/exclusion criteria specified that participants had to have laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR test) diagnosed  $\leq 72$  hours of randomization and had experienced COVID-19 symptoms for  $< 7$  days prior to randomization. Mild-to-moderate disease was defined as: participants had to maintain oxygen saturation  $\geq 93\%$  breathing room air, not have been previously or currently hospitalized for treatment of COVID-19; were experiencing at least one of the following symptoms at randomization: fever, cough, shortness of breath. Prior or current use of putative COVID-19 treatments (e.g., corticosteroids, convalescent plasma, or remdesivir) was an exclusion criterion. The study treatment was administered on Day 1. Participants were followed for 28 days.

An initial interim analysis was done on the first 275 symptomatic participants. A subsequent analysis was performed on all 799 symptomatic participants (first 275 plus the next 524 symptomatic participants in phase 2) in phase 1 and 2. The results from all 799 symptomatic patients in phase 1 and 2, submitted in response to FDA's request, serve as the basis of review for this EUA application.

Table 3 displays demographics and baseline characteristics, which were well balanced between the treatment groups. The median age was 42 years with 7% of subjects ages 65 years or older, and 2% who were 75 years of age or older. Approximately half the participants were female, and half the participants were Hispanic or Latino while under 10% were Black or African American. Approximately 31% of subjects reported at least 1 severe symptom at baseline, 36% reported at least 1 moderate symptom and no severe symptoms, and 13% reported only mild symptoms.

Slightly over 60% of participants met at least one protocol-specified high risk criteria for COVID-19 progression which were >50 years of age, BMI >30 kg/m<sup>2</sup>, cardiovascular disease including hypertension, chronic lung disease including asthma, chronic metabolic disease including diabetes, chronic kidney disease including those on dialysis, chronic liver disease, and immunosuppressed. Approximately, 34% were considered as high risk according to the following criteria outlined in the EUA Fact Sheet: ≥65 years of age, BMI ≥35 kg/m<sup>2</sup>, chronic kidney disease, diabetes, immunosuppressive disease, or current receipt of immunosuppressive treatment, or were ≥55 years of age and had at least one of the following: cardiovascular disease, hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease. The median duration of symptoms was 3 days. Approximately 38% of participants were seropositive for the SARS-CoV-2 virus at baseline as determined by positive Euroimmune IgA, Euroimmune IgG, or Abbot Architect IgG assay.

The pre-specified primary efficacy analysis population was the modified full analysis set (mFAS) including 665 randomized participants with a positive central-lab determined RT-qPCR from nasopharyngeal (NP) swab samples at randomization. One hundred thirty-four randomized participants were excluded from the mFAS because they had negative or missing RT-qPCR data. The participant demographics and baseline characteristics for mFAS were similar to those for all randomized participants.

**Table 3: Baseline Demographics and Disease Characteristics in Trial R10933-10987-COV-2067 (All Randomized)**

	<b>2400 mg casirivimab and imdevimab N=266</b>	<b>8000 mg casirivimab and imdevimab N=267</b>	<b>Placebo N=266</b>
Female	144 (54%)	147 (55%)	132 (50%)
Hispanic or Latino	132 (50%)	134 (50%)	137 (52%)
Black or African American	27 (10%)	23 (9%)	24 (9%)
Age (median years)	42	42	42
Age >50 years	80 (30%)	76 (28%)	78 (29%)
BMI >30 kg/m <sup>2</sup>	101 (38%)	104 (39%)	93 (35%)
Duration of symptoms (days, mean)	4	3	3
Viral load (mean, log <sub>10</sub> copies/mL)	5.23	5.05	5.21
Seropositive	96 (36%)	102 (38%)	106 (40%)

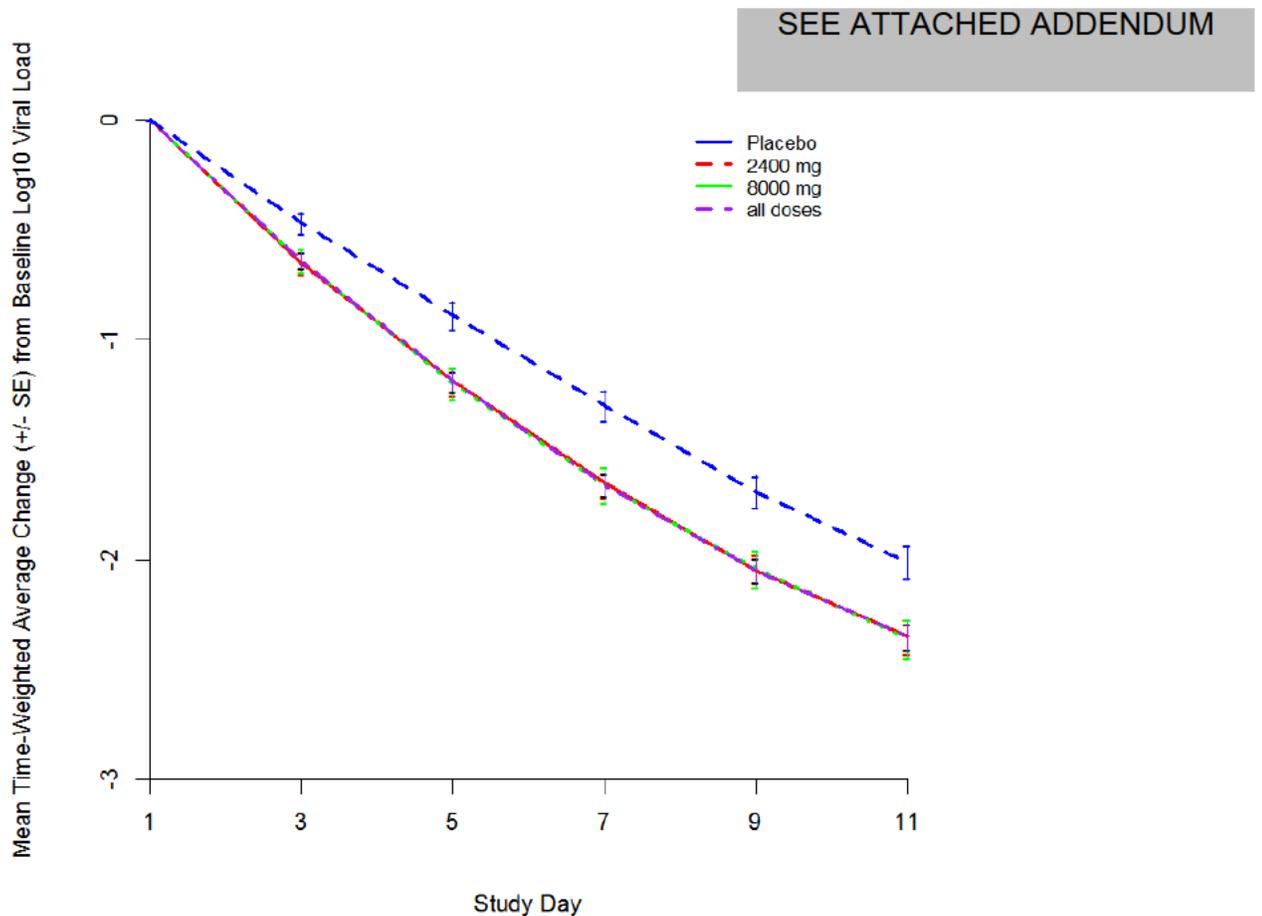
Source: EUA Request Tables 14.1.1.1-1-ALL and 14.1.1.4-1-ALL

### Efficacy Analyses – Virologic Endpoints

The prespecified primary endpoint in phase 1 and 2 was the time-weighted average (TWA) change from baseline in viral shedding ( $\log_{10}$  copies/mL), as measured by RT-qPCR in nasopharyngeal swab samples. The Agency agreed with this endpoint for phase 1 and 2 analyses. For phase 3 trials, FDA generally recommends the use of clinical endpoints reflecting how a patient feels, functions, and survives.

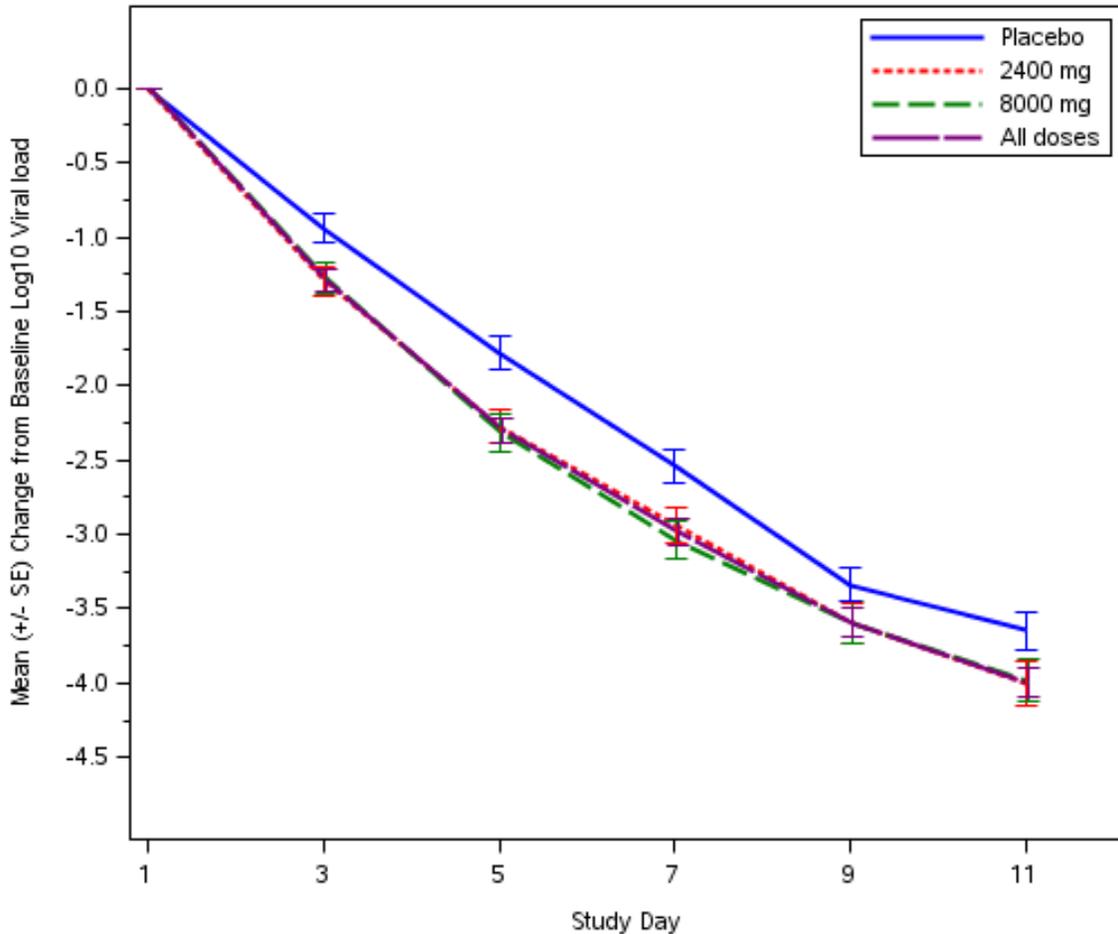
Overall, the difference in TWA change from Day 1 through Day 7 for the pooled doses of casirivimab and imdevimab compared with placebo in mFAS was -0.36 copies/mL ( $p < 0.0001$ ) (Figure 1). Likewise for mean change from baseline viral load, larger reductions were observed with casirivimab and imdevimab compared to placebo (Figure 2). The time point for the Applicant's primary virologic endpoint (i.e., Day 7) is appropriate for detecting effects on viral load parameters.

**Figure 1: Time-weighted Average Change from Baseline Viral Load ( $\log_{10}$  copies/mL) (Modified Full Analysis Set)**



Source: Statistical reviewer's plot based on EUA 91 Regulatory Response submitted November 09, 2020 Table 10.1

**Figure 2: Mean Change from Baseline Viral Load ( $\log_{10}$  copies/mL) (Modified Full Analysis Set)**

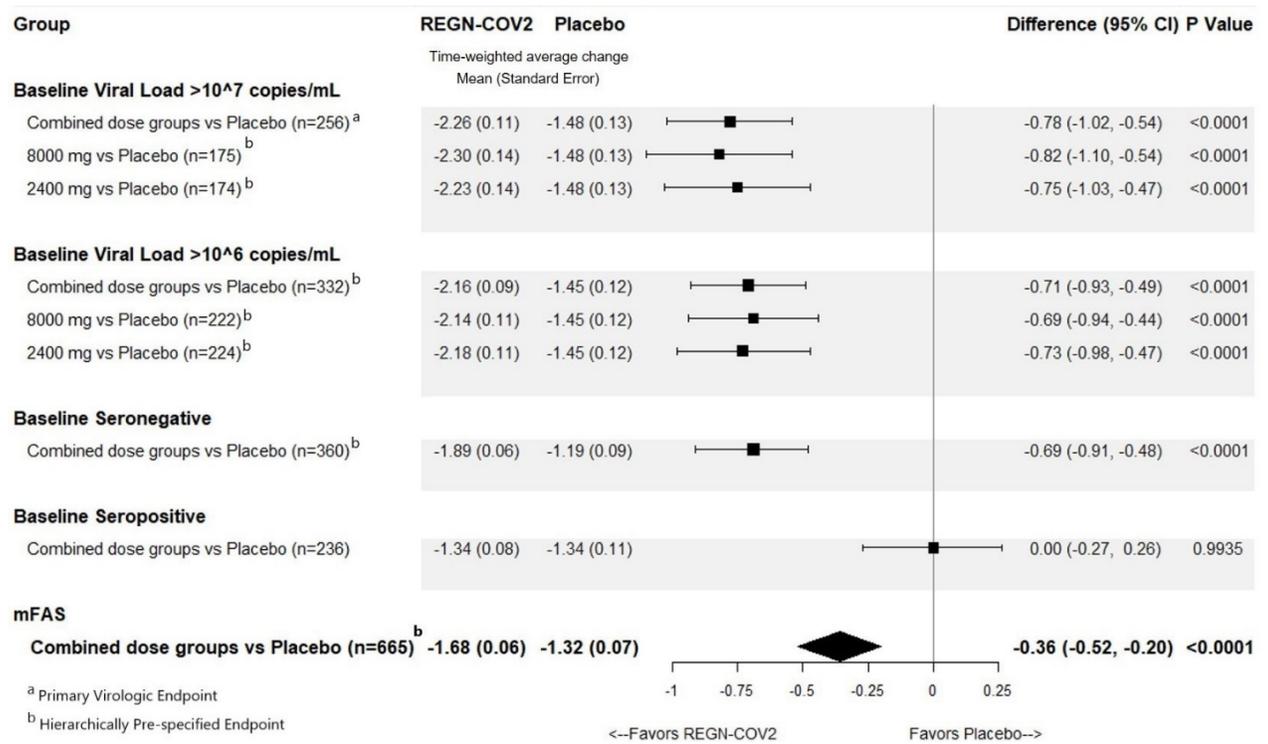


Source: EUA 91 Regulatory Response submitted via email November 19, 2020

The Applicant conducted subgroup analyses which showed a greater magnitude of change from baseline in viral load in subgroups with high baseline viral load  $>10^7$  copies/mL, high baseline viral load  $>10^6$  copies/mL, and participants who were seronegative at baseline (see Figure 3). The largest reductions in viral load relative to placebo occurred in patients with high viral load (-0.78  $\log_{10}$  copies/mL) or who were seronegative at baseline (-0.69  $\log_{10}$  copies/mL). In subjects who were seropositive at baseline, no difference was noted in viral load reduction in the combined casirivimab and imdevimab dose groups and placebo.

SEE ATTACHED ADDENDUM

**Figure 3: Subgroup Analysis – TWA Change from Baseline Viral Load (log<sub>10</sub> copies/mL) (Modified Full Analysis Set)**



<sup>a</sup> Primary Virologic Endpoint

<sup>b</sup> Hierarchically Pre-specified Endpoint

<sup>a</sup> Primary Virologic Endpoint

<sup>b</sup> Hierarchically Pre-specified hypothesis tests

Seronegative was defined as no measurable anti-spike IgG, anti-spike IgA, and anti-nucleocapsid IgG and seropositive was defined as measurable anti-spike IgG, anti-spike IgA, and/or anti-nucleocapsid IgG.

Source: EUA 91 Regulatory Response submitted November 09, 2020 and statistical reviewer

### Efficacy Analyses – Clinical Outcomes

While the viral load analyses were agreed to as the primary endpoint in the phase 1 and 2 part of the trial, the most important clinically meaningful endpoint in outpatient trials is COVID-19-related hospitalizations or emergency room (ER) visits within 28 days after treatment. Reliable evidence of a treatment effect on this endpoint would provide a strong basis for efficacy conclusions.

A prespecified secondary endpoint was the proportion of participants with at least one COVID-19-related medically attended visit (MAV) through day 29. The MAVs were defined based on hospitalizations, emergency room (ER) visits, urgent care visits, or physician office visits or telemedicine visits that were assessed by the investigator as related to COVID-19.

### Medically Attended Visits

There were no deaths, and there were 27 unique participants with COVID-19-related MAVs in the mFAS. A lower proportion of casirivimab and imdevimab-treated participants had a COVID-19 related medically attended visit compared to

the placebo-treated participants (Table 4). The treatment difference for all (pooled) doses was statistically significantly superior to placebo. It should be noted that some of these MAV events were telemedicine visits for relatively minor symptoms, and were not necessarily representative of clinically important disease progression.

**Table 4: Proportion of Subjects with Events of COVID-19-Related Medically Attended Visits Within Day 28 (mFAS)**

Group	Events n/N (%)	Placebo - casirivimab and imdevimab difference	95% CI <sup>a</sup>	p-value <sup>b</sup>
Placebo	15/231 (6.5%)			
2400 mg <sup>c</sup> casirivimab and imdevimab	6/215 (2.8%)	3.7%	-0.3% to 8.0%	0.0754
8000 mg <sup>d</sup> Casirivimab and imdevimab	6/219 (2.7%)	3.8%	-0.2% to 8.0%	0.0737
All doses	12/434 (2.8%)	3.7%	0.6% to 7.9%	0.0240

<sup>a</sup>Confidence intervals were from the Miettinen-Nurminen method.

<sup>b</sup>The two-sided p-values were from Fisher's exact test.

<sup>c</sup>2400 mg (1200 mg casirivimab and 1200 mg imdevimab)

<sup>d</sup>8000 mg (4000 mg casirivimab and 4000 mg imdevimab)

Source: EUA 91 Request Table 14.2.2.1-6M and statistical reviewer

### *Hospitalizations and Emergency Room Visits*

Among COVID-19-related MAV events, events of hospitalization or emergency room visits were most representative of severe COVID-19 disease, and considered important from a clinical perspective and from a public health standpoint. The Applicant conducted post-hoc analyses to assess treatment effects in the subset of MAVs consisting of only hospitalizations and ER visits. A lower proportion of casirivimab and imdevimab-treated participants progressed to COVID-19-related hospitalization or emergency room visits compared to the placebo-treated participants (Table 5).

**Table 5: Proportion of Subjects with Events of COVID-19-Related Hospitalization or Emergency Room Visits Within 28 Days After Treatment (mFAS)**

Group	Events n/N (%)	Placebo - casirivimab and imdevimab difference	95% CI <sup>a</sup>	p-value <sup>b</sup>
Placebo	10/231 (4.3%)			
2400 mg <sup>c</sup> casirivimab and imdevimab	4/215 (1.9%)	2.5%	-0.9% to 6.2%	0.1766
8000 mg <sup>d</sup> casirivimab and imdevimab	4/219 (1.8%)	2.5%	-0.8% to 6.2%	0.1749
All doses	8/434 (1.8%)	2.5%	-0.1% to 6.1%	0.0778

<sup>a</sup>Confidence intervals were from the Miettinen-Nurminen method

<sup>b</sup>The two-sided p-values were from Fisher's exact test.

<sup>c</sup>2400 mg (1200 mg casirivimab and 1200 mg imdevimab)

<sup>d</sup>8000 mg (4000 mg casirivimab and 4000 mg imdevimab)  
 Source: EUA 91 Request Table 14.2.2.1-6M and statistical reviewer

### *Hospitalizations and Emergency Room visits in High Risk Subgroup*

The Applicant also conducted a post-hoc analysis showing that most COVID-19-related hospitalizations or emergency room visits occurred in patients classified as high risk for hospitalization. This high risk subgroup was classified as having at least one of the following: age  $\geq 65$  years, BMI  $\geq 35$  kg/m<sup>2</sup>, chronic kidney disease, diabetes, immunosuppressive disease, or current receipt of immunosuppressive treatment. Participants were also considered high risk if they were  $\geq 55$  years of age and had at least one of following: cardiovascular disease, hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease. This analysis suggested that the difference in event rates between active treatment groups and the placebo group may be larger on the absolute scale in high risk participants (Table 6). For this reason, the EUA authorization is restricted to high risk outpatients who meet these specific criteria. Likewise, a trend favoring casirivimab and imdevimab compared to placebo was also observed in the subgroup analysis using the protocol-specified high risk definition.

**Table 6: Proportion of Subjects with Events of Hospitalization or Emergency Room Visits Within 28 Days After Treatment for Subjects Who Were at Higher Risk of Hospitalization (mFAS)**

Group	Events n/N (%)	Placebo - casirivimab and imdevimab difference	95% CI <sup>a</sup>	p-value <sup>b</sup>
Placebo	7/78 (9.0%)			
2400 mg <sup>c</sup> casirivimab and imdevimab	2/70 (2.9%)	6.1%	-2.0% to 15.0%	0.1721
8000 mg <sup>d</sup> casirivimab and imdevimab	2/81 (2.5%)	6.5%	-0.8% to 15.3%	0.0944
All doses	4/151 (2.6%)	6.3%	0.5% to 15.0%	0.0485

<sup>a</sup>Confidence intervals were from the Miettinen-Nurminen method

<sup>b</sup>The two-sided p-values were from Fisher's exact test.

<sup>c</sup>2400 mg (1200 mg casirivimab and 1200 mg imdevimab)

<sup>d</sup>8000 mg (4000 mg casirivimab and 4000 mg imdevimab)

Sources: EUA 91 Regulatory Response submitted November 10, 2020 and statistical reviewer

In considering the benefit-risk profile of casirivimab and imdevimab in the high risk population defined by FDA, it is useful to estimate the number needed to treat to prevent one COVID-19-related hospitalization or emergency room visit. The estimated difference in event rates between the pooled casirivimab and imdevimab group and the placebo group in Table 6 corresponds to a number needed to treat of under 16 outpatients. While this would likely outweigh risks from anticipated adverse events such as hypersensitivity and infusion-related reactions, there is statistical uncertainty about this benefit as the nominal 95% confidence interval is wide, with needing to treat between 7 and 200 high risk

patients to prevent one event. This uncertainty stems from the relatively small sample size and number of events.

Table 7 displays key characteristics of participants with COVID-19 related hospitalizations or emergency room visits in participants with high risk factors. As there were only 11 participants with these clinical events, efficacy conclusions based on this analysis is not robust to small changes in event counts due to missing data or adjudications. Two participants required hospitalization in the casirivimab and imdevimab group, three participants required hospitalization in the placebo group, and the remaining 6 participants (2 casirivimab and imdevimab; and 4 placebo) required ER visits without hospitalization.

**Table 7: Listing of High Risk Participants with COVID-19-Related Hospitalizations or Emergency Room Visits**

Treatment	Age	Risk factor	Gender	Event Start (Day)	Type of Event	Reason (COVID-19 related per Investigator)
Placebo	77	DM, Hypertension	F	3	Hosp.	Hypoxemia
Placebo	62	Hypertension	F	10	ER	Fever, shortness of breath
Placebo	42	DM, BMI 40	M	2	Hosp.	Pneumonia
Placebo	89	DM, BMI 35	F	11	Hosp.	Worsening of COVID-19, acute respiratory failure
Placebo	37	DM	F	15	ER	Shortness of breath
Placebo	48	Immunosuppressed	F	5	ER	Vomiting, abdominal pain
Placebo	27	DM	F	11	ER	Hypertension, tachycardia
2400 mg	82	DM, Hypertension	F	3	Hosp.	Pneumonia
2400 mg	38	DM	F	11	ER	Nausea, vomiting, abdominal pain
8000 mg	37	BMI 42	F	2	ER	Shortness of breath
8000 mg	20	DM, BMI 52	M	1	Hosp.	Shortness of breath, worsening COVID-19 infection

Abbreviations: BMI = body mass index (kg/m<sup>2</sup>); DM = diabetes mellitus; ER = emergency room visit; Hosp. = hospitalization

Source: EUA 91 SN7 Appendix A and Response to FDA information request

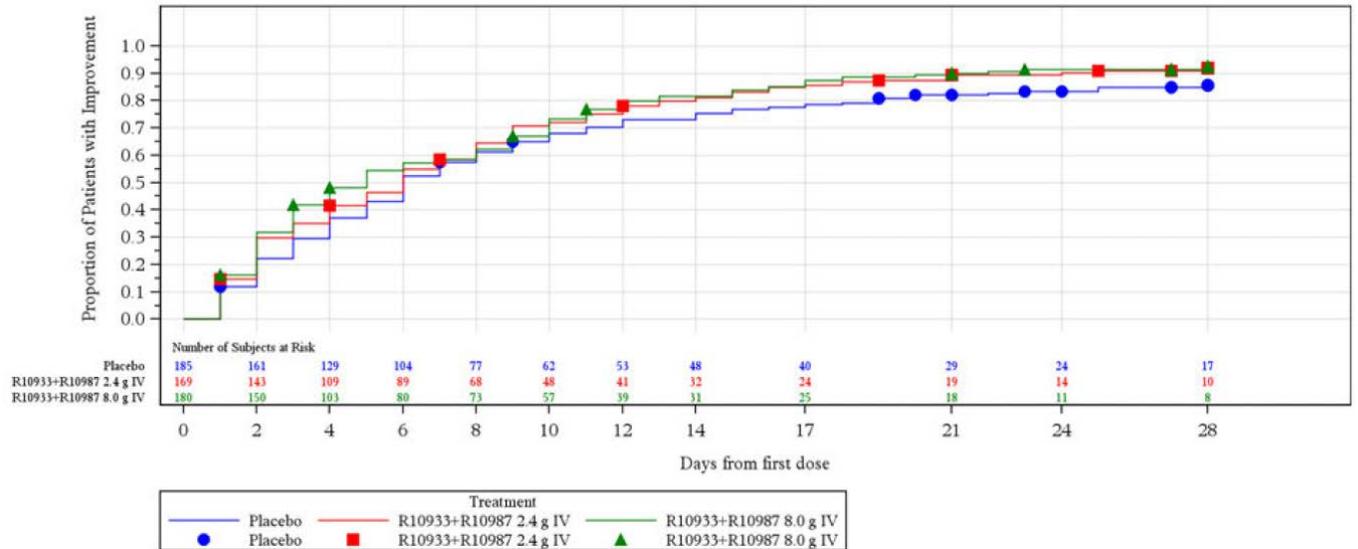
### Assessment of Effects on COVID-19 Symptoms

Additional prespecified exploratory endpoints were based on symptom measurements, although it is currently unclear what symptom-based endpoint would be optimal for COVID-19 outpatient trials. Trial participants used a daily questionnaire to rate their symptoms as 0 = none or absent, 1 = mild, 2 = moderate, or 3 = severe. Symptoms assessed were shortness of breath or difficulty breathing, chills, feverish, sore throat, cough, nausea, vomiting, diarrhea, headache, red or watery eyes, body and muscle aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomach ache, rash, sneezing, sputum/phlegm, runny nose.

Figure 4 displays time to symptom improvement defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent postbaseline. In the

mFAS population, the median time to symptom improvement was 5 days for the combined casirivimab and imdevimab dose groups, as compared to 6 days for placebo group; this difference was nominally statistically significant (p=0.019).

**Figure 4: Time to Symptom Improvement (mFAS)**



Source: EUA 91 Request submitted November 10, 2020 Figure FDA 14.2

The median time to first day of symptom resolution was 14 days for casirivimab and imdevimab compared to 16 days for placebo. Symptom resolution was defined as all symptoms rated by participants to be absent.

### *Time from Symptom Onset*

The mean duration of symptoms prior to treatment was 3 days in both treatment groups and 4 days in the placebo group. Approximately 99% of participants were treated within 7 days of symptom onset. Clinically significant trends or differences in outcomes based on time from symptom onset to the time of dosing were not identified by the Applicant. The limitations with this analysis are acknowledged, specifically, there were relatively few MAV endpoints in each subset for time from symptom onset (onset by Day 3, onset by Day 5, and onset by Day 7).

### Clinical Efficacy Conclusions

Overall, phase 1 and 2 analysis from COV-2067 provided evidence that casirivimab and imdevimab, administered together, may be effective for the treatment of high risk COVID-19 outpatients. In particular, a potential benefit was seen for the outcome of COVID-19 related hospitalizations or emergency room visits in participants with high risk factors such as  $\geq 65$  years of age, BMI  $\geq 35$  kg/m<sup>2</sup>, chronic kidney disease, diabetes, immunosuppressive disease, currently receiving immunosuppressive treatment, or age  $\geq 55$  years of age and at least one risk factor of cardiovascular disease, or hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease, which is clinically

meaningful and is considered both an individual patient and public health benefit. Results were also suggestive of reduced time to symptom improvement, and reduced time to symptom resolution with casirivimab and imdevimab. Clinical efficacy data did not show a dose-response relationship for casirivimab and imdevimab, which supported authorization of the dose of 1200 mg casirivimab and 1200 mg imdevimab.

SEE ATTACHED ADDENDUM

While the efficacy data support that casirivimab and imdevimab may be effective for the treatment of COVID-19 in high risk outpatients, there are limitations and uncertainties to these findings. Limitations included multiplicity issues when considering secondary endpoints, relying on post-hoc analysis of the prespecified endpoint of medically attended visits, the relatively small number of hospitalization events, and statistical uncertainty surrounding the number needed to treat to prevent serious clinical worsening.

#### Analysis of spike protein variants

In trial COV-2067, interim data identified only one substitution (G446V) occurring in the receptor binding domain at an allele fraction  $\geq 15\%$ , which was detected in 3/66 subjects who had nucleotide sequencing data, each at a single time point (two at baseline in subjects from placebo and 2400 mg casirivimab + imdevimab groups, and one at Day 25 in a subject from the 8000 mg casirivimab + imdevimab group). The G446V variant had reduced susceptibility to imdevimab of 135-fold compared to wild-type in a pseudoparticle neutralization assay but was susceptible to casirivimab and the casirivimab + imdevimab.

## **IX. Clinical Safety**

Casirivimab and imdevimab, administered together, are being evaluated in clinical trials in adults with confirmed COVID-19, individuals who are uninfected but at risk of acquiring SARS-COV-2 infection, and healthy volunteer adults. Overall, more than 2100 clinical trial participants, both non-hospitalized and hospitalized, have received casirivimab and imdevimab intravenously at doses 2400 mg or 8000 mg.

For the proposed EUA, the safety of casirivimab and imdevimab is based on interim data from the phase 1/2 trial in 799 ambulatory (non-hospitalized) adult participants with COVID-19. The adverse events collected were infusion-related reactions and hypersensitivity reactions of moderate severity or higher through day 29, all serious adverse events (SAEs); and in phase 1 only, all grade 3 and 4 treatment-emergent adverse events (TEAEs). Adverse events of special interest (AESI) consisted of infusion-related adverse events and hypersensitivity reactions.

## Trial R10933-10987-COV-2067 Results

### *Overall Exposure for Safety Analysis in COV-2067*

The safety analysis is based on data from 518 subjects dosed with IV casirivimab and imdevimab, either the 2400 mg dose (1200 mg per mAb) (n=258) or 8000 mg dose (4000 mg per mAb) (n=260) compared with 262 subjects randomized to placebo.

### *Safety Overview*

SEE ATTACHED ADDENDUM

As displayed in Table 8 below, no deaths were reported. Serious adverse events (SAEs) were reported in fewer participants in casirivimab and imdevimab treatment groups (1.6% or 0.8%) compared to placebo (2.3%). Grade 3 or 4 TEAEs were reported in fewer participants in the casirivimab and imdevimab treatment groups compared to placebo in phase 1. No participants withdrew from the study due to TEAEs. However, two participants receiving 8000 mg casirivimab and imdevimab experienced infusion-related reactions resulting in permanent discontinuation of the infusion compared to one participant in the placebo arm who permanently discontinued infusion due to an infusion-related reaction.

**Table 8: Safety Overview in COV-2067**

	<b>2400 mg IV casirivimab and imdevimab (N=258)</b>	<b>8000 mg IV casirivimab and imdevimab (N=260)</b>	<b>Placebo (N=262)</b>
Deaths	0	0	0
Participants with ≥1 serious adverse event	4 (1.6%)	2 (0.8%)	6 (2.3%)
Participants with Grade 3 or 4 SAEs	3 (1.2%)	2 (0.8%)	4 (1.5%)
Participants with TEAE resulting in study withdrawal	0	0	0
Participants with any AE of special interest (AESI), grade 2 or higher	0	4 (1.5%)	2 (0.8%)
Participants with AESI leading to permanent discontinuation of infusion	0	2 (0.8%)	1 (0.4%)

Source: EUA 91 SN7 and response to FDA IR dated November 4, 2020

### *Serious Adverse Events*

A total of 13 serious adverse events (SAE) were reported in 12 subjects. Serious adverse events were reported in 4 subjects (1.6%) in the casirivimab and imdevimab 2400 mg group, 2 subjects (0.8%) in the casirivimab and imdevimab 8000 mg group, and 6 subjects (2.3%) in the placebo group. None of the SAEs were assessed by the investigators to be related to study drug. The SAEs that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia,

nausea and vomiting (2400 mg casirivimab and imdevimab), intestinal obstruction and dyspnea (8000 mg) and COVID-19, pneumonia and hypoxia (placebo). The table below outlines the SAEs by System Organ Class.

**Table 9: Treatment-Emergent Serious Adverse Events by System Organ Class**

	<b>2400 mg IV casirivimab and imdevimab (N=258)</b>	<b>8000 mg IV casirivimab and imdevimab (N=260)</b>	<b>Placebo (N=262)</b>
<b>Participants with ≥1 SAE</b>	4 (1.6%)	2 (0.8%)	6 (2.3%)
<b>Gastrointestinal disorders</b>	2 (0.8%)	1 (0.4%)	0
Vomiting	1 (0.4%)	0	0
Nausea	1 (0.4%)	0	0
Intestinal obstruction	0	1 (0.4%)	0
<b>Respiratory, thoracic and mediastinal disorders</b>	1 (0.4%)	1 (0.4%)	2 (0.8%)
Hypoxia	0	0	2 (0.8%)
Dyspnea	0	1 (0.4%)	0
Pneumonia	1 (0.4%)	2 (0.8%)	0
<b>Infections and infestations</b>	1 (0.4%)	1 (0.4%)	0
COVID-19	0	1 (0.4%)	0
COVID-19 pneumonia	1 (0.4%)	0	0
<b>Metabolism and nutrition disorders</b>	1 (0.4%)	0	0
Hyperglycemia	1 (0.4%)	0	0
<b>Vascular disorders</b>	0	0	1 (0.4%)
Hypertension	0	0	1 (0.4%)

Source: EUA 91 SN7

### *Laboratory Findings*

Safety laboratory assessments performed during the treatment period were provided to the site investigators and site staff. Only clinically significant laboratory abnormalities that fulfilled one of the targeted TEAEs or AESI were recorded in the Applicant's database and included in EUA submissions. The Applicant reports that no safety laboratory abnormality led to either study or study treatment discontinuation. One participant that was randomized to the 2400 mg casirivimab and imdevimab group experienced a clinically significant laboratory abnormality that was reported as a targeted TEAE. This participant with a past history of pre-diabetes experienced a grade 3 SAE of hyperglycemia on study day 5 with blood glucose value of 505 mg/dL.

### *Long-Term Follow-Up Safety*

There is no long-term safety information available after day 29.

## Analysis of Submission-Specific Safety Issues

### *Infusion-related Reactions*

Infusion-related reactions, of grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8000 mg (4000 mg casirivimab and 4000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and include pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm and none were reported in the 2400 mg (1200 mg casirivimab and 1200 mg imdevimab) arm. All events were grade 2 in severity.

In two subjects receiving the 8000 mg dose of casirivimab and imdevimab, the infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. The adverse events reported were grade 2 in severity. The events began during infusion administration (approximately 15 – 60 minutes after start of infusions). The events resolved following administration of oral diphenhydramine.

### *Hypersensitivity Reactions*

There were no hypersensitivity reactions reported in either of the 2400 mg or 8000 mg casirivimab and imdevimab dose groups. Hypersensitivity events were reported in two participants in the placebo group in phase 1 and 2. The reported hypersensitivity events were dizziness, vomiting and headache (n=1) and rash (n=1) in the placebo group. These AEs were Grade 2 in severity and assessed as drug-related by the investigator.

### *Anaphylaxis*

While no anaphylaxis events were observed in COV-2067, one participant in the hospitalized trial R10933-10987-COV-2066 developed a possible anaphylactic reaction: A 63-year-old hospitalized patient, requiring low-flow oxygen at randomization, was reported to develop an anaphylactic reaction approximately 55 minutes after completion of the 8000 mg IV infusion. The participant developed shortness of breath, chills, diaphoresis, hypoxia, tachycardia; and was placed on BIPAP, transferred to the intensive care unit (ICU), and treated with dexamethasone, epinephrine, and diphenhydramine. The event had resolved, and the patient was discharged from the ICU the following day, still requiring supplemental oxygen but no longer requiring high flow oxygen support.

In summary, infusion-related reactions including those requiring permanent discontinuation of the infusion and a possible anaphylactic reaction were observed with casirivimab and imdevimab. In light of the serious nature of hypersensitivity reactions including anaphylaxis and infusion-related reactions, the review team has determined to include warning statements in the Fact Sheet

for healthcare providers to communicate this potential risk including appropriate management, should such reactions occur.

#### *Immune Response Attenuation*

Administration of casirivimab and imdevimab may attenuate the endogenous immune response to SARS-CoV-2 and potentially make patients more susceptible to re-infection. Similarly, casirivimab and imdevimab administration could reduce the response to SARS-CoV-2 vaccination, though no data are available at this time to address these possible risks.

#### *Anti-Drug Antibodies*

Bridging assays to screen for and confirm the presence of anti-drug antibody (ADA) in patient serum samples are under development. Separate assays will be used to test for ADA specific to each antibody (casirivimab and imdevimab). Method qualification or validation data for immunogenicity assays are not yet available. The Applicant will bank serum samples for ADA analysis once the validated assays are available. In principle, the testing approach and method format is appropriate to evaluate ADA incidence, specificity, and titer provided the methods are qualified as fit for purpose. Assays to characterize neutralizing activity of potential ADA may be developed based on an overall immunogenicity risk-assessment. The proposed immunogenicity assay and strategy are acceptable to support the EUA.

#### *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 in outpatients with mild to moderate disease. The risk of ADE was addressed by the Applicant in completed non-clinical cell culture studies (Please see Section XIII, Nonclinical Data to Support Efficacy for more information related to ADE). The applicability of the findings from these nonclinical studies to the clinical setting is not known. While there was no evidence of enhanced disease in participants treated with casirivimab and imdevimab in Trial COV-2067, there is still a theoretical possibility of increased incidence of reinfection or enhanced disease if infected again once mAb concentrations have waned to sub-neutralizing concentrations in casirivimab and imdevimab-treated patients.

#### Experience in Trials in Hospitalized Patients

Available information from ongoing casirivimab and imdevimab trials in hospitalized patients or other antiviral mAb trials in hospitalized COVID-19 patients were considered during review of this EUA application. The key findings, which are relevant to the current review, are summarized below.

- *R10933-10987-COV-2066* – This is an ongoing trial of casirivimab and imdevimab in hospitalized adults with COVID-19. On October 30, 2020 the study Independent Data Monitoring Committee (IDMC) recommended pausing enrollment of patients who require mechanical ventilation (Cohort 3), and patients on high flow oxygen or noninvasive ventilation (Cohort 2). The recommendation was based on a potential safety signal and an unfavorable risk/benefit profile for Cohorts 2 and 3.

The IDMC recommended continuing enrollment in the remaining study cohorts 1A and 1 in the hospitalized trial COV-2066 i.e., patients requiring no supplemental oxygen (or on room air) or patients with oxygen saturation >93% on low-flow oxygen via nasal cannula, simple face mask, or other similar device. The IDMC also recommended continuing enrollment in other populations, namely, the outpatient trial COV-2067, the postexposure prophylaxis trial COV-2069, and the healthy volunteer trial COV-2093.

- *RECOVERY Hospitalized Trial* – The trial Data Monitoring Committee (DMC) reviewed the safety and efficacy data available for 15,545 patients randomized in the non-IND RECOVERY trial, that is ongoing in the United Kingdom, including 325 patients recruited in the casirivimab and imdevimab arm versus control comparison. The DMC did not identify a reason to modify the protocol or enrollment in the study.

In addition, the FDA is aware of a public statement from the DSMB providing oversight of the ACTIV-3 trial in hospitalized patients that no additional patients will receive LY-CoV555, another monoclonal antibody to the spike protein of SARS-CoV-2. The DSMB recommended no further randomization to LY-CoV555 treatment based on a low likelihood that this intervention would be of clinical value in the hospitalized patient population.

Taking together, recommendations from two separate data monitoring committees for casirivimab and imdevimab hospitalized trials, and following consultation with experts from the Division of Pulmonary, Allergy and Critical Care in Office of New Drugs, CDER, we have determined that, at the present time, the scope of authorization should be well-defined regarding the specific patient population.

Our review of the data supports inclusion of a Limitations of Authorized Use as follows:

#### LIMITATIONS OF AUTHORIZED USE

- Casirivimab and imdevimab are 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.
- Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

## **X. Specific Populations**

### Rationale for Inclusion of Adolescent Patients under EUA

As of November 12, 2020, over 1 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/>). 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  $\geq 40$  kg, and the safety profile, there is a prospect of benefit for this patient population.

Based on the totality of evidence to support the prospect of benefit and that it is reasonable to believe the known and potential benefits outweigh the known and potential risks, the authorization of casirivimab and imdevimab includes adolescents who are 12 years of age and older and who weigh at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization (BMI  $\geq 85$ th percentile for age and gender, or sickle cell disease, or congenital or acquired heart disease, or neurodevelopmental disorders, or a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), or asthma, reactive airway or other chronic respiratory disease that requires daily medication for control). To date, casirivimab and imdevimab have not been administered in pediatric patients; however, ongoing clinical trials are beginning to enroll adolescents.

### Dosing Considerations for Special Populations

- Safety and pharmacokinetic (PK) data are not available in children, pregnant women, lactating women, patients with renal insufficiency, or patients with hepatic insufficiency. 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

PK profiles of casirivimab and imdevimab are consistent with the profile of other IgG monoclonal antibodies. PK samples were analyzed currently using an LC/MS/MS method, known to be associated with low sensitivity and interference.

SEE ATTACHED ADDENDUM

### Rationale for dosing recommendations

- Analysis of data from trial COV-2067 showed similar response with doses of 1200 and 4000 mg of each monoclonal antibody for virology, symptomatology, or reduction in hospitalizations or emergency room visits. Therefore, the dose of 1200 mg casirivimab and 1200 mg imdevimab is recommended, administered as a single IV infusion over a minimum of 60 minutes.
- The Applicant stated that the 1200 mg casirivimab and 1200 mg imdevimab doses are predicted to achieve lung concentrations above the *in vitro* EC<sub>99</sub> values for live virus neutralization (0.14 and 0.80 µg/mL for casirivimab and imdevimab, respectively) for at least 28 days, assuming a lung to serum concentration ratio of 15%. It should be noted that there are uncertainties in the EC<sub>99</sub> values and the prediction of a lung to serum ratio of 15%, which was based on one publication (Magyarics, 2019). However, even using a more conservative estimate for the lung to serum concentration ratio (e.g., less than 5% partition), it is still predicted to achieve concentrations above *in vitro* EC<sub>90</sub> (0.03 and 0.08 µg/mL for casirivimab and imdevimab, respectively) for several weeks.

### Rationale for dosing recommendations in pediatric patients and other specific populations

- Pediatric patients: The PK of casirivimab and imdevimab in pediatric patients have not been evaluated. 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 trial COV-2067.

- 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, based on body surface area, is 7.5 relative to the proposed human dose of 1200 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 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<sub>50</sub> 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<sub>50</sub> values in the low nanomolar to picomolar range. Casirivimab, imdevimab and the casirivimab + imdevimab combination mediated concentration-dependent ADCP with human macrophages, with EC<sub>50</sub> 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 pVSV-SARS-CoV-2-S, VSV-SARS-CoV-2-S virus, and SARS-CoV-2 entry into Vero or Vero E6 cells, with EC<sub>50</sub> and EC<sub>90</sub> values in the picomolar range. Against SARS-CoV-2, the neutralization EC<sub>50</sub> values of casirivimab, imdevimab and the casirivimab + imdevimab combination were 37.4 pM, 42.1 pM and 31.0 pM, respectively, and the EC<sub>90</sub> values were 178 pM, 430 pM and 173 pM, respectively.
- Neutralization activity of casirivimab, imdevimab and the casirivimab + imdevimab combination was evaluated against VSV pseudotyped with 37 different RBD variants identified as the most common RBD variations in circulation as of late March 2020, and D614G, D614N spike protein variants. The median neutralization EC<sub>50</sub> values for casirivimab, imdevimab and the casirivimab + imdevimab combination were 50 pM (n=39; range: 11-208 pM), 27 pM (n=39; range: 5-16,900 pM) and 31 pM (n=23; range: 5-61 pM), respectively. Neutralization EC<sub>50</sub> values were increased by approximately 4.5-fold for casirivimab against the G476S variant and the S494P variant and by 463-fold for imdevimab against the N439K variant. The casirivimab + imdevimab combination retained activity against all variants tested.
- Escape variants were identified following passage in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following passage in the presence of the casirivimab + imdevimab combination. Variants which

showed reduced susceptibility to casirivimab included K417E, Y453F, L455F, F486V and Q493K substitutions. Variants which showed reduced susceptibility to imdevimab included K444Q and V445A substitutions. Each variant showing reduced susceptibility to one mAb retained susceptibility to the other, and all variants retained susceptibility to the casirivimab + imdevimab combination.

- The potential of casirivimab and of imdevimab to mediate viral entry was assessed in immune cell lines co-incubated with recombinant vesicular stomatitis virus (VSV) pseudoparticles expressing SARS-CoV-2 spike protein at concentrations of mAb(s) down to approximately 20-fold below the respective neutralization EC<sub>50</sub> values. The casirivimab + imdevimab combination and imdevimab alone, but not casirivimab alone, mediated entry of pseudoparticles into FcγR2<sup>+</sup> Raji and FcγR1<sup>+</sup>/FcγR2<sup>+</sup> 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. Only the treatment studies are relevant to the indication sought (Table 10).

**Table 10: Relevant Studies of the Product in Animal Models of Disease**

Study Number	IND, BLA, or Literature Reference	Type of Study <sup>2</sup>	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	<a href="#">Baum et al., 2020</a>	Treatment Non-GLP	Rhesus macaques (n=4 in each group)	Animals inoculated intranasally and intratracheally with 1x10 <sup>6</sup> PFU of SARS-CoV-2 and treated 1-day post-infection with casirivimab + imdevimab or an isotype control (placebo).	25 mg/kg or 150 mg/kg casirivimab + imdevimab dosed intravenously. 5-day study.	Complete
N/A	<a href="#">Baum et al., 2020</a>	Treatment Non-GLP	Syrian golden hamster (aged 6-8 weeks, n=50 total)	Animals inoculated intranasally with 2.3 x 10 <sup>4</sup> PFU SARS-CoV-2 and treated 1-day post-infection with casirivimab + imdevimab or an isotype control (placebo).	0.5, 5 or 50 mg/kg casirivimab + imdevimab dosed intraperitoneally. 7-day study.	Complete; additional study planned

PFU=plaque-forming units.

<sup>2</sup> 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.

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 impact of treatment with casirivimab + imdevimab administered together on viral genomic RNA (gRNA) and sub-genomic RNA (sgRNA) in nasopharyngeal swabs and oral swabs was evaluated on Days 0, 1, 2, 4 6 and 7 (virus inoculation = Day 0, drug administration = Day 1). Lung histopathology was assessed at the end of study.

Compared to placebo-treated animals, animals treated with casirivimab + imdevimab displayed accelerated viral clearance in both nasopharyngeal and oral swabs samples, including both genomic and sub-genomic RNA, at both doses of the mAbs administered together. 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.

The 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](#)). In a treatment study with casirivimab and imdevimab administered together, animals dosed with 50 mg/kg and 5 mg/kg doses of casirivimab + imdevimab 1-day post viral challenge showed protection from weight loss. Detailed viral load data were not reported, but high genomic RNA and sub-genomic RNA levels in the lungs of a few treated animals were observed, so the antiviral activity was not clear in this treatment model.

#### **XIV. Supply Information**

- Quantity of drug product needed for one treatment course per individual for proposed EUA indication (adults, pediatrics): 2400 mg (1200 mg of casirivimab and 1200 mg of imdevimab) administered as a single dose intravenous infusion
- A total of (b) (4) treatment courses are anticipated to be available by the end of year 2020. The number of treatment courses expected to be available in 2021 are (b) (4) in Q1 2021, and (b) (4) in Q2 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).

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. 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). The DP is manufactured at (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 DS manufacturing process consists of (b) (4).  
The DP manufacturing process consists of (b) (4) and inspection and packaging. 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 5°C. 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 5°C 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 5°C and (b) (4) at the accelerated storage condition of 25°C/60% RH. Results from a (u) (4) stability study at the stress condition of 45°C further support expiry dating. The stability protocol is 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), 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 11: Manufacturing Sites**

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

(b) (4)	IND-148069	Regeneron Pharmaceuticals, Inc.	(b) (4)	Acceptable
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## XVII. Clinical Trial Site Inspections

Clinical site inspections were not conducted for this EUA.

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

Nonclinical site inspections were not conducted for this EUA.

## XIX. Recommendations From Treatment Guidelines and Other Sources

- Bamlanivimab was authorized for emergency use on November 9, 2020 as monotherapy for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.
- No specific therapy is suggested for patients with COVID-19 who are not hospitalized in any of the following COVID-19 Treatment Guidelines:
  - The Centers for Disease Control (CDC) notes that clinical management of COVID-19 includes infection prevention and control measures as well as supportive care, which includes hospitalization for supplemental oxygen and mechanical ventilatory support when indicated. Remdesivir has been approved for the treatment of COVID-19 in certain hospitalized patients (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html>; updated November 2, 2020).
  - The Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 Infection (<https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management>; updated September 25, 2020) provides 12 recommendations related to the treatment of COVID-19. IDSA does not recommend any specific therapy for the treatment of patients with mild to moderate disease who are not hospitalized.
  - The NIH COVID-19 Treatment Guidelines (<https://www.covid19treatmentguidelines.nih.gov/>; updated November 3, 2020) reviews various treatments for COVID-19 and the associated available evidence. No specific antiviral or immunomodulatory therapy is recommended for patients who are not hospitalized or are hospitalized but do not require supplemental oxygen

<https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/>; updated October 9, 2020).

## **XX. Risk-Benefit Assessment and Recommendations for Emergency Use**

Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that bind to non-overlapping epitopes on 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 are currently being evaluated in phase 1, 2 and 3 clinical trials for both prophylaxis and treatment indications.

Based on review of the topline data from a planned analysis of combined phase 1 and 2 in R10933-10987-COV-2067 (NCT04425629), an ongoing randomized, double-blind, placebo-controlled, phase 1/2/3 trial of casirivimab and imdevimab in ambulatory patients (nonhospitalized) with mild to moderate COVID-19, it is reasonable to believe that casirivimab and imdevimab, administered together, may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization; and that the known and potential benefits of casirivimab and imdevimab outweigh the known and potential risks of the drug for the recommended authorized use.

The primary endpoint for the phase 1 and 2 analysis in trial R10933-10987-COV-2067 was a virologic endpoint; and the time-weighted average change from baseline of SARS-CoV-2 nasopharyngeal viral load at Day 7 was statistically significant for the combined dose groups. The median time to symptom improvement as recorded in a trial specific daily symptom diary was 5 days for casirivimab and imdevimab subjects, as compared to 6 days for placebo subjects. The predefined secondary endpoint of medically attended visits consisted of hospitalizations, emergency room visits, urgent care visits, or physician office/telemedicine visits for COVID-19. COVID-19 medically attended visits were reported in a lower proportion of participants in all casirivimab and imdevimab dose groups compared to placebo. However, the most clinically meaningful outcome supporting the conclusion that the drug may be effective for the proposed authorized use was from a post-hoc analysis of the proportion of participants with COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. When considering only individuals at high risk for progression to severe disease (classified as  $\geq 65$  years of age, BMI  $\geq 35$  kg/m<sup>2</sup>, chronic kidney disease, diabetes, immunosuppressive disease, current receipt of immunosuppressive treatment, or  $\geq 55$  years of age and had at least one of cardiovascular disease, hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease), hospitalization or emergency room visits

were reported in 9% of participants in the placebo group compared to 3% in the combined casirivimab and imdevimab dose groups.

With respect to prevention of hospitalizations among high risk patients with mild to moderate COVID-19, the estimated number needed to treat is 16. However, there is uncertainty around this estimate of benefit due to a small number of events. This uncertainty is acceptable in the current setting in the U.S. with more than 100,000 new positive tests per day and hospitals at risk for exceeding bed and/or intensive care unit capacity in a number of U.S. regions. Based on placebo data in R10933-10987-COV-2067, the risk of hospitalization in high risk patients is approximately 9%. Reducing this risk offers benefit to individual patients and could ameliorate a significant burden on the public health system to respond to the pandemic.

The dose-response relationship analyses based on results from trial R10933-10987-COV-2067 support the dose of 1200 mg casirivimab and 1200 mg imdevimab. A flat dose-response relationship for efficacy was identified for two doses (1200 mg casirivimab and 1200 mg imdevimab; 4000 mg casirivimab and 4000 mg imdevimab), based on viral load and clinical outcomes. In addition, the dose of 1200 mg casirivimab and 1200 mg imdevimab is expected to achieve concentrations in lung tissues above the *in vitro* EC<sub>90</sub> values for 28 days.

Regarding assessment of the known and potential risks, the overall safety database of casirivimab and imdevimab is comprised of more than 2100 COVID-19 patients who have received an IV infusion of casirivimab and imdevimab at doses ranging from 1200 to 4000 mg for each mAb; with 518 participants who received a single dose of 1200 mg casirivimab and 1200 mg imdevimab or higher in trial R10933-10987-COV-2067. The major adverse events of concern were hypersensitivity reactions including anaphylaxis and infusion-related reactions. These were not observed in patients who received 1200 mg casirivimab and 1200 mg imdevimab; and these were infrequent and were considered to be moderate when patients were administered the 4000 mg casirivimab and 4000 mg imdevimab. In order to mitigate the risk of significant hypersensitivity reactions including anaphylaxis and infusion-related reactions, patients receiving casirivimab and imdevimab should be clinically monitored during the infusion and for at least 1 hour after the infusion is complete. Casirivimab and imdevimab should be administered in settings in which health care providers would have immediate access to medications to treat a severe infusion reaction such as anaphylaxis and the ability to activate the emergency medical system (EMS) as necessary.

Some cartons and vials labeled for investigational use (and not EUA use) may be used in the interim for supply purposes. Cartons and vials labeled for investigational use may state 'For Intravenous or Subcutaneous Use' on the respective carton or vial label. The potential risk of incorrect dosing route was considered in the context of the available product supply and the surge in

COVID-19 cases in the U.S. As casirivimab and imdevimab must be administered together by intravenous infusion only under this EUA, the following steps were taken to mitigate inadvertent incorrect dosing: prominent display of 'Intravenous (IV) Infusion only' in the Healthcare Provider Fact Sheet, revision of the Fact Sheet Directions document that physically accompanies carton packaging, and a recommendation to the Applicant to issue a Dear HealthCare Provider (DHCP) Letter to communicate the issue, provide visual depictions of the available types of cartons and vials for use under EUA, and provide assistance via hotline and their dedicated EUA website.

The emergence of viral variants following treatment with casirivimab and imdevimab was infrequent in the phase 1 and 2 analysis (observed in 1 out of 66 trial participants for whom sequencing data were available). However, the clinical trials are ongoing, and the clinical relevance of treatment-emergent viral resistance is not known. Given that treatment-emergent resistant variants may arise and their relative fitness is not known, and because patients could continue to shed virus after treatment, patients should continue to self-isolate and use infection control measures (e.g. wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines in order minimize the spread of SARS-CoV-2.

The FDA carefully considered findings available or reported from trials of hospitalized patients treated with casirivimab and imdevimab or other anti-spike monoclonal antibodies. As the benefit of casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19 and its use may be associated with risk of worse clinical outcomes in patients with severe or critical COVID-19, casirivimab and imdevimab will not be authorized for 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 individuals with an underlying non-COVID-19 related comorbidity that requires chronic oxygen therapy.

While bamlanivimab has been authorized for emergency use by FDA for the treatment of mild to moderate COVID-19 in adults and pediatric patients who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, there remains a relative unmet need based on the latest COVID-19 surge with over 100,000 new positive tests diagnosed daily in the U.S.

Based on the totality of the evidence available to the FDA and considering the context of the current public health emergency in the U.S., it is reasonable to believe that casirivimab and imdevimab may be effective for the proposed authorized use and the known and potential benefits of casirivimab and imdevimab outweigh the known and potential risks of the drug. Therefore, the Review Division and the Office of Infectious Diseases conclude that the statutory

standards are met and recommend authorization of an EUA for casirivimab and imdevimab, administered together, for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

## **XXI. Considerations for Adverse Event (AE) Monitoring**

This product will either be used in clinical trials or in clinical practice. If used in clinical trials conducted under IND, FDA IND safety reporting regulations will apply. 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 "Casirivimab and Imdevimab Treatment 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 their plan for distribution of the Fact Sheet for Health Care Providers and Fact Sheet for Patients and Parents and Caregivers is as follows:

- The products will be accompanied with a 1-Page information sheet, referred to as Fact Sheet Directions, placed in each shipping container that will include details about the EUA products, and describe how to access the Fact Sheets via an Applicant-managed URL and QR code. The Applicant plans to distribute the 1-page Fact Sheet Direction document in the shipment containers sent to the pharmacy and each shipment container will contain a sufficient quantity of the Directions to supply one sheet per dose. In other words, a shipment container may contain 32 to 227 treatment doses and will be accompanied by an equal number of 1-page Fact Sheet Directions.

- For supply under EUA of products manufactured with the EUA labels, the carton label will include a URL and QR code to direct healthcare providers and recipients to the Fact Sheets, in lieu of physically co-packaging the Fact Sheets with the vial carton.
- The URL is [www.REGENCOV2.com](http://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)
- Fact Sheet for Patients and Parents/Caregivers (See Section XXVI. Appendices)
- Information Sheet, referred to as Fact Sheet Directions, accompanying each shipping container (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. Information Sheet, referred to as Fact Sheet Directions
4. Dear Healthcare Provider Letter

## FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF CASIRIVIMAB AND IMDEVIMAB

### AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products casirivimab and imdevimab to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

### LIMITATIONS OF AUTHORIZED USE

- Casirivimab and imdevimab are 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.
- Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

Casirivimab and imdevimab have been authorized by FDA for the emergency uses described above.

Casirivimab and imdevimab are not FDA-approved for these uses.

Casirivimab and imdevimab are authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of casirivimab and imdevimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Casirivimab and imdevimab carton and vial labels may instead be labeled REGN10933 and REGN10987 respectively.

**This EUA is for the use of the unapproved products, casirivimab and imdevimab, to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization [see *Limitations of Authorized Use*].**

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI)  $\geq 35$
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are  $\geq 65$  years of age

- Are ≥55 years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 – 17 years of age AND have
  - BMI ≥85th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](https://www.cdc.gov/growthcharts/clinical_charts.htm), OR
  - sickle cell disease, OR
  - congenital or acquired heart disease, OR
  - neurodevelopmental disorders, for example, cerebral palsy, OR
  - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

**CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY  
INTRAVENOUS (IV) INFUSION ONLY.**

Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to casirivimab and imdevimab. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

- The authorized dosage is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous (IV) infusion as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.
- Casirivimab and imdevimab solutions must be diluted prior to administration.
- Administer 1,200 mg of casirivimab and 1,200 mg of imdevimab together as a single IV infusion over at least 60 minutes via pump or gravity.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.
- Patients treated with casirivimab and imdevimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of casirivimab and imdevimab in COVID-19, please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

**Contraindications**

None.

**Dosing**

## **CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.**

### Patient Selection and Treatment Initiation

This section provides essential information on the unapproved products, casirivimab and imdevimab, for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization [*see Limitations of Authorized Use*].

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI)  $\geq 35$
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are  $\geq 65$  years of age
- Are  $\geq 55$  years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 – 17 years of age AND have
  - BMI  $\geq 85$ th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](https://www.cdc.gov/growthcharts/clinical_charts.htm), OR
  - sickle cell disease, OR
  - congenital or acquired heart disease, OR
  - neurodevelopmental disorders, for example, cerebral palsy, OR
  - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

### Dosage

The dosage in adults and in pediatric patients (12 years of age and older weighing at least 40 kg) is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous infusion over at least 60 minutes. Casirivimab and imdevimab solutions must be diluted prior to administration. Casirivimab and imdevimab should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

### Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating women and in patients with renal impairment [*see Full EUA Prescribing Information, Use in Specific Populations (11)*].

## **Preparation and Administration**

### Preparation

Casirivimab and imdevimab are each supplied in individual single-dose vials. Casirivimab and imdevimab solutions must be diluted prior to administration.

Casirivimab and imdevimab solution for 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 solution must be discarded, and fresh solution prepared.
  - The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.
3. Obtain an IV infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. Withdraw and discard 20 mL of 0.9% Sodium Chloride Injection from the infusion bag prior to adding casirivimab and imdevimab solutions according to [Table 1](#).
4. Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial using two separate syringes and dilute together in the infusion bag containing 0.9% Sodium Chloride Injection, see [Table 1](#). Discard any product remaining in the vial.
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake.** 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 and at room temperature up to 25°C (77°F) for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Casirivimab and imdevimab carton and vial labels may instead be labeled REGN10933 and REGN10987 respectively.

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

	Antibody Dose	Volume to Withdraw from Vial	Number of Vials Needed <sup>b</sup>	Volume of 0.9% Sodium Chloride to Discard from a 250 mL Infusion Bag	Total Volume for Infusion	Maximum Infusion Rate	Minimum Infusion Time
Casirivimab and Imdevimab 2,400 mg Dose <sup>a</sup>	Casirivimab REGN10933  1,200 mg	10 mL	1 vial of 11.1 mL <b>OR</b> 4 vials of 2.5 mL	20 mL	250 mL	250 mL/hr	60 minutes
	Imdevimab REGN10987  1,200 mg	10 mL	1 vial of 11.1 mL <b>OR</b> 4 vials of 2.5 mL				

NOTE: casirivimab = REGN10933; imdevimab = REGN10987

<sup>a</sup> 1,200 mg of Casirivimab and 1,200 mg of Imdevimab are to be administered together as a single intravenous infusion for a combined 2,400 mg dose.

<sup>b</sup> One 11.1 mL vial of one antibody may be prepared with four 2.5 mL vials of the other antibody to create one treatment course.

### Administration

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 IV bag.
- Prime the infusion set.
- Administer as an IV infusion via pump or gravity over at least 60 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see [Table 1](#)).
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush with 0.9% Sodium Chloride Injection.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

### **Storage**

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the individual original carton to protect from light. Do NOT freeze, shake, or expose to direct light.

### **Warnings**

There are limited clinical data available for casirivimab and imdevimab. Serious and unexpected adverse events may occur that have not been previously reported with casirivimab and imdevimab use.

#### Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions have been observed with administration of casirivimab and imdevimab.

Signs and symptoms of infusion-related reactions may include:

- fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

#### Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients

requiring high flow oxygen or mechanical ventilation with COVID-19. Therefore, casirivimab and imdevimab are not authorized for use in patients *[see Limitations of Authorized Use]*:

- 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.

#### **Side Effects**

Adverse events have been reported with casirivimab and imdevimab *[see Full EUA Prescribing Information, Clinical Trials Experience (6.1)]*.

Additional adverse events associated with casirivimab and imdevimab, some of which may be serious, may become apparent with more widespread use.

#### **INSTRUCTIONS FOR HEALTH CARE PROVIDERS**

As the health care provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the “Fact Sheet for Patients, Parents and Caregivers” (and provide a copy of the Fact Sheet) prior to the patient receiving casirivimab and imdevimab, including:

- FDA has authorized the emergency use of casirivimab and imdevimab to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.
- The patient or parent/caregiver has the option to accept or refuse casirivimab and imdevimab.
- The significant known and potential risks and benefits of casirivimab and imdevimab, and the extent to which such risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with casirivimab and imdevimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of casirivimab and imdevimab related to COVID-19, please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

## **MANDATORY REQUIREMENTS FOR CASIRIVIMAB AND IMDEVIMAB UNDER EMERGENCY USE AUTHORIZATION:**

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of casirivimab and imdevimab to be administered together, the following items are required. Use of casirivimab and imdevimab under this EUA is limited to the following (all requirements **must** be met):

1. 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 progressing to severe COVID-19 and/or hospitalization [*see Limitations of Authorized Use*].
2. As the health care provider, communicate to your patient or parent/caregiver, as age appropriate, information consistent with the “Fact Sheet for Patients, Parents and Caregivers” prior to the patient receiving casirivimab and imdevimab. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient’s medical record that the patient/caregiver has been:
  - a. Given the “Fact Sheet for Patients, Parents and Caregivers”,
  - b. Informed of alternatives to receiving casirivimab and imdevimab, and
  - c. Informed that casirivimab and imdevimab are unapproved drugs that are authorized for use under this Emergency Use Authorization.
3. Patients with known hypersensitivity to any ingredient of casirivimab and imdevimab must not receive casirivimab and imdevimab.
4. The prescribing health care provider and/or the provider’s designee are/is responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of casirivimab and imdevimab.
5. The prescribing health care provider and/or the provider’s designee are/is responsible for mandatory reporting of all medication errors and serious adverse events\* potentially related to casirivimab and imdevimab treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words “Casirivimab and imdevimab treatment under Emergency Use Authorization (EUA)” in the description section of the report.
  - Submit adverse event reports to FDA MedWatch using one of the following methods:
    - Complete and submit the report online: [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm), or
    - By using a postage-paid Form FDA 3500 (available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
    - Call 1-800-FDA-1088 to request a reporting form
    - Submitted reports should include in the field name, “Describe Event, Problem, or Product Use/Medication Error” a statement “Casirivimab and imdevimab treatment under Emergency Use Authorization (EUA).”

\*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

## 6. OTHER REPORTING REQUIREMENTS

In addition, please provide a copy of all FDA MedWatch forms to:

Regeneron Pharmaceuticals, Inc

Fax: 1-888-876-2736

E-mail: [medical.information@regeneron.com](mailto:medical.information@regeneron.com)

Or call Regeneron Pharmaceuticals at 1-844-734-6643 to report adverse events.

## APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternatives to casirivimab and imdevimab to be administered together for patients who have mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization. Additional information on COVID-19 treatments can be found at <https://www.cdc.gov/coronavirus/2019-ncov/index.html>. The health care provider should visit <https://clinicaltrials.gov/> to determine whether the patient may be eligible for enrollment in a clinical trial.

## AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. FDA has issued this EUA, requested by Regeneron Pharmaceuticals, Inc. for the unapproved products, casirivimab and imdevimab, to be administered together, for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.<sup>1</sup> As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

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<sup>1</sup> The health care provider should visit <https://clinicaltrials.gov/> to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that casirivimab and imdevimab, administered together, may be effective for the treatment of COVID-19 in patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for casirivimab and imdevimab will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

#### **CONTACT INFORMATION**

For additional information visit [www.REGENCOV2.com](http://www.REGENCOV2.com)

If you have questions, please contact Regeneron at 1-844-734-6643.

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**END SHORT VERSION FACT SHEET**

**Long Version Begins on Next Page**

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## FULL EUA PRESCRIBING INFORMATION

### FULL EUA PRESCRIBING INFORMATION: CONTENTS\*

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## 1 AUTHORIZED USE

Casirivimab and imdevimab are authorized to be administered together for use under an EUA for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

### LIMITATIONS OF AUTHORIZED USE

- Casirivimab and imdevimab are 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.
- Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19 [see *Warnings and Precautions (5.2)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Patient Selection

The optimal dosing regimen for treatment of COVID-19 has not yet been established.

The recommended dosing regimen may be updated as data from clinical trials become available.

#### **CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.**

##### Patient Selection and Treatment Initiation

This section provides essential information on the unapproved products, casirivimab and imdevimab, to be administered together, for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization [*see Limitations of Authorized Use*].

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI)  $\geq 35$
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are  $\geq 65$  years of age
- Are  $\geq 55$  years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 – 17 years of age AND have
  - BMI  $\geq 85$ th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](https://www.cdc.gov/growthcharts/clinical_charts.htm), OR
  - sickle cell disease, OR
  - congenital or acquired heart disease, OR
  - neurodevelopmental disorders, for example, cerebral palsy, OR
  - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

## 2.2 Dosage

The dosage in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous infusion. Casirivimab and imdevimab solutions must be diluted prior to administration.

Casirivimab and imdevimab should be given as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

## 2.3 Dose Adjustment in Specific Populations

### Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women [see *Use in Specific Populations (11.1, 11.2)*].

### Pediatric Use

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 are not recommended for pediatric patients weighing less than 40 kg or those less than 12 years of age [see *Use in Specific Populations (11.3)*].

### Renal Impairment

No dosage adjustment is recommended in patients with renal impairment [see *Use in Specific Populations (11.5)*].

## 2.4 Dose Preparation and Administration

### Preparation

Casirivimab and imdevimab are each supplied in individual single-dose vials. Casirivimab and imdevimab solutions must be diluted prior to administration.

Casirivimab and imdevimab infusion solution 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 solution must be discarded, and fresh solution prepared. The solution for each vial should be clear to slightly opalescent, colorless to pale yellow.

- Obtain an IV infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. Withdraw and discard 20 mL of 0.9% Sodium Chloride Injection from the infusion bag prior to adding casirivimab and imdevimab according to [Table 2](#).
- Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial using two separate syringes and dilute together in the infusion bag containing 0.9% Sodium Chloride Injection, see [Table 2](#). Discard any product remaining in the vial.
- Gently invert infusion bag by hand approximately 10 times. **Do not shake.**

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 and at room temperature up to 25°C (77°F) for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

**Table 2: Recommended Dilution Instructions for Casirivimab and Imdevimab for IV Infusion**

	Antibody Dose	Volume to Withdraw from Vial	Number of Vials Needed <sup>b</sup>	Volume of 0.9% Sodium Chloride to Discard from a 250 mL Infusion Bag	Total Volume for Infusion	Maximum Infusion Rate	Minimum Infusion Time
Casirivimab and Imdevimab 2,400 mg Dose <sup>a</sup>	Casirivimab REGN10933 1,200 mg	10 mL	1 vial of 11.1 mL <b>OR</b> 4 vials of 2.5 mL	20 mL	250 mL	250 mL/hr	60 minutes
	Imdevimab REGN10987 1,200 mg	10 mL	1 vial of 11.1 mL <b>OR</b> 4 vials of 2.5 mL				

**NOTE: casirivimab = REGN10933; imdevimab = REGN10987**

<sup>a</sup> 1,200 mg of Casirivimab and 1,200 mg of Imdevimab are to be administered together as a single intravenous infusion for a combined 2,400 mg dose.

<sup>b</sup> One 11.1 mL vial of one antibody may be prepared with four 2.5 mL vials of the other antibody to create one treatment course.

### Administration

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 IV bag.

- Prime the infusion set.
- Administer as an IV infusion via pump or gravity over at least 60 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see [Table 2](#)).
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush with 0.9% Sodium Chloride Injection.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

### Storage

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 and at room temperature up to 25°C (77°F) for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration

## **3 DOSAGE FORMS AND STRENGTHS**

Casirivimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:

- Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) in a single-dose vial

Imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:

- Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) in a single-dose vial

**Casirivimab** and **imdevimab** carton and vial labels may instead be labeled **REGN10933** and **REGN10987** respectively.

## **4 CONTRAINDICATIONS**

None.

## 5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for casirivimab and imdevimab. Serious and unexpected adverse events may occur that have not been previously reported with casirivimab and imdevimab use.

### 5.1 Hypersensitivity Reactions including Anaphylaxis and Infusion-Related Reactions

There is a potential for serious hypersensitivity reactions, including anaphylaxis, with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions have been observed with administration of casirivimab and imdevimab.

Signs and symptoms of infusion related reactions may include:

- fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

### 5.2 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19. Therefore, casirivimab and imdevimab are not authorized for use in patients *[see Limitations of Authorized Use]*:

- 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.

## 6 OVERALL SAFETY SUMMARY

Overall more than 2,100 subjects have been exposed to IV casirivimab and imdevimab in clinical trials in both hospitalized and non-hospitalized patients.

## 6.1 Clinical Trials Experience

The safety of casirivimab and imdevimab is based on analysis from one phase 1/2 trial of 799 ambulatory (non-hospitalized) subjects with COVID-19.

R10933-10987-COV-2067 is a randomized, double-blind, placebo-controlled clinical trial in ambulatory adults with mild to moderate COVID-19 symptoms who had a sample collected for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion. Subjects were treated with a single infusion of 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) (N=258) or 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) (N=518), or placebo (n=262). The adverse events collected were infusion-related reactions and hypersensitivity reactions of moderate severity or higher through day 29, all serious adverse events (SAEs); and in phase 1 only, all grade 3 and 4 treatment-emergent adverse events.

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

### Hypersensitivity Including Anaphylaxis and Infusion-related Reactions

One anaphylactic reaction was reported in the clinical program. The event began within 1 hour of completion of the infusion, and required treatment including epinephrine. The event resolved. Infusion-related reactions, of grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and include pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm and none were reported in the 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm.

In two subjects receiving the 8,000 mg dose of casirivimab and imdevimab, the infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. All events resolved [*see Warnings and Precautions (5.1)*].

## 7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete [*see Warnings and Precautions (5.1) and Clinical Trials Experience (6.1)*].

## 8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of casirivimab and imdevimab are ongoing [see *Overall Safety Summary (6)*].

Completion of FDA MedWatch Form to report all medication errors and serious adverse events\* occurring during casirivimab and imdevimab use and considered to be potentially related to casirivimab and imdevimab is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

\*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of casirivimab and imdevimab, the prescribing health care provider and/or the provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm), or
- Use a postage-paid Form FDA 3500 (available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form

**IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:**

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of casirivimab and imdevimab
- Pertinent laboratory and virology information

- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In section A, box 1, provide the patient's initials in the Patient Identifier
2. In section A, box 2, provide the patient's date of birth or age
3. In section B, box 5, description of the event:
  - a. Write "Casirivimab and imdevimab treatment under Emergency Use Authorization (EUA)" as the first line
  - b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In section G, box 1, name and address:
  - a. Provide the name and contact information of the prescribing health care provider or institutional designee who is responsible for the report
  - b. Provide the address of the treating institution (NOT the health care provider's office address).

## 9 OTHER REPORTING REQUIREMENTS

In addition, please provide a copy of all FDA MedWatch forms to:

Regeneron Pharmaceuticals, Inc

Fax: 1-888-876-2736

E-mail: [medical.information@regeneron.com](mailto:medical.information@regeneron.com)

Or call Regeneron Pharmaceuticals at 1-844-734-6643 to report adverse events.

## 10 DRUG INTERACTIONS

Casirivimab and imdevimab are 2 monoclonal antibodies (mAbs) which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

## 11 USE IN SPECIFIC POPULATIONS

### 11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Casirivimab and imdevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with casirivimab and imdevimab. In a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, no binding of clinical concern was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

## **11.2 Nursing Mothers**

### Risk Summary

There are no available data on the presence of casirivimab and/or imdevimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for casirivimab and imdevimab and any potential adverse effects on the breastfed child from casirivimab and imdevimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

## **11.3 Pediatric Use**

The safety and effectiveness of casirivimab and imdevimab have not been assessed in pediatric patients. The recommended dosing regimen is expected to result in comparable serum exposures of casirivimab and imdevimab in patients 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in Trial R10933-10987-COV-2067.

## **11.4 Geriatric Use**

Of the 799 patients with SARS-CoV-2 infection randomized in Trial R10933-10987-COV-2067, 7% were 65 years or older, and 2% were 75 years of age or older. The difference in PK of casirivimab and imdevimab in geriatric patients compared to younger patients is unknown.

## 11.5 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.

## 11.6 Hepatic Impairment

The effect of hepatic impairment on PK of casirivimab and imdevimab is unknown.

## 11.7 Other Specific Populations

The effect of other covariates (e.g., sex, race, body weight, disease severity) on PK of casirivimab and imdevimab is unknown.

## 12 OVERDOSAGE

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

## 13 PRODUCT DESCRIPTION

Casirivimab, a human immunoglobulin G-1 (IgG1) monoclonal antibody (mAb), is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 145.23 kDa.

Casirivimab injection is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution in a single-dose vial for intravenous infusion after dilution available as a 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) solution and must be administered with imdevimab.

- Casirivimab: Each 2.5 mL of solution contains 300 mg of casirivimab, L-histidine (1.9 mg), L-histidine monohydrochloride monohydrate (2.7 mg), polysorbate 80 (2.5 mg), sucrose (200 mg), and Water for Injection, USP. The pH is 6.0.
- Casirivimab: Each 11.1 mL of solution contains 1,332 mg of casirivimab, L-histidine (8.3 mg), L-histidine monohydrochloride monohydrate (12.1 mg), polysorbate 80 (11.1 mg), sucrose (888 mg), and Water for Injection, USP. The pH is 6.0.

Imdevimab, a human IgG1 mAb, is a covalent heterotetramer consisting of 2 heavy chains and 2 light chains produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture and has an approximate molecular weight of 144.14 kDa.

Imdevimab injection is a sterile, preservative-free, clear to slightly opalescent and colorless to pale yellow solution in a single-dose vial for intravenous infusion after dilution available as a 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) solution and must be administered with casirivimab.

- Imdevimab: Each 2.5 mL of solution contains 300 mg of imdevimab, L-histidine (1.9 mg), L-histidine monohydrochloride monohydrate (2.7 mg), polysorbate 80 (2.5 mg), sucrose (200 mg), and Water for Injection, USP. The pH is 6.0.
- Imdevimab: Each 11.1 mL of solution contains 1,332 mg of imdevimab, L-histidine (8.3 mg), L-histidine monohydrochloride monohydrate (12.1 mg), polysorbate 80 (11.1 mg), sucrose (888 mg), and Water for Injection, USP. The pH is 6.0.

## 14 CLINICAL PHARMACOLOGY

### 14.1 Mechanism of Action

Casirivimab (IgG1 $\kappa$ ) and imdevimab (IgG1 $\lambda$ ) are two recombinant human mAbs which are unmodified in the Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants  $K_D$  = 45.8 pM and 46.7 pM, respectively. Casirivimab, imdevimab and the casirivimab + imdevimab combination blocked RBD binding to the human ACE2 receptor with  $IC_{50}$  values of 56.4 pM, 165 pM and 81.8 pM, respectively [see [Microbiology/Resistance Information \(15\)](#)].

### 14.2 Pharmacodynamics

Trial R10933-10987-COV-2067 evaluated casirivimab and imdevimab with doses of 1 and 3.33 times the recommended doses (1,200 mg casirivimab and 1,200 mg imdevimab; 4,000 mg casirivimab and 4,000 mg imdevimab) in ambulatory patients with COVID-19. A flat dose-response relationship for efficacy was identified for casirivimab and imdevimab at those two doses, based on viral load and clinical outcomes.

### 14.3 Pharmacokinetics

Pharmacokinetic profiles of casirivimab and imdevimab are expected to be consistent with the profile of other IgG1 mAbs.

#### Specific Populations

The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of casirivimab and imdevimab is unknown. Renal impairment is not expected to impact the PK of casirivimab and imdevimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of casirivimab and imdevimab.

#### Drug-Drug Interactions

Casirivimab and imdevimab are mAbs which are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that

are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely [see *Drug Interactions (10)*].

## 15 MICROBIOLOGY/RESISTANCE INFORMATION

### Antiviral Activity

In a SARS-CoV-2 virus neutralization assay in Vero E6 cells, casirivimab, imdevimab, and the casirivimab + imdevimab combination neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC<sub>50</sub> values of 37.4 pM (0.006 µg/mL), 42.1 pM (0.006 µg/mL), and 31.0 pM (0.005 µg/mL) respectively.

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

### Antibody Dependent Enhancement (ADE) of Infection

The potential of casirivimab and of imdevimab to mediate viral entry was assessed in immune cell lines co-incubated with recombinant vesicular stomatitis virus (VSV) pseudoparticles expressing SARS-CoV-2 spike protein at concentrations of mAb(s) down to approximately 10-fold below the respective neutralization EC<sub>50</sub> values. The casirivimab + imdevimab combination and imdevimab alone, but not casirivimab alone, mediated entry of pseudoparticles into FcγR2<sup>+</sup> Raji and FcγR1<sup>+</sup>/FcγR2<sup>+</sup> 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).

### Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to the casirivimab + imdevimab combination.

Escape variants were identified following passage in cell culture of recombinant VSV encoding SARS-CoV-2 spike protein in the presence of casirivimab or imdevimab individually, but not following passage in the presence of the casirivimab + imdevimab combination. Variants which showed reduced susceptibility to casirivimab included spike protein amino acid substitutions K417E, Y453F, L455F, F486V and Q493K, and variants which showed reduced susceptibility to imdevimab included K444Q and V445A substitutions. Each variant showing reduced susceptibility to one mAb retained susceptibility to the other, and all variants retained susceptibility to the casirivimab + imdevimab combination.

In neutralization assays using VSV pseudotyped with 37 different receptor binding domain (RBD) variants identified as the most common RBD variations in circulation as of late March 2020, and D614G, D614N spike protein variants, casirivimab had reduced susceptibility (4.5-fold) to G476S and S494P variants, and imdevimab had reduced susceptibility (463-fold) to the N439K variant. The casirivimab + imdevimab combination retained activity against all variants tested.

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

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

#### Immune Response Attenuation

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

## **16 NONCLINICAL TOXICOLOGY**

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

In a toxicology study in cynomolgus monkeys, casirivimab and imdevimab had no adverse effects when administered intravenously. Non-adverse liver findings (minor transient increases in AST and ALT) were observed.

In tissue cross-reactivity studies with casirivimab and imdevimab using human adult and fetal tissues, no binding of clinical concern was detected.

## **17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA**

The casirivimab + imdevimab combination has been assessed in rhesus macaque and Syrian golden hamster treatment models of SARS-CoV-2 infection. Therapeutic administration of the casirivimab + imdevimab combination at 25 mg/kg or 150 mg/kg into rhesus macaques (n=4 for each dosing group) 1-day post infection resulted in approximately 1-2 log<sub>10</sub> reductions in genomic and sub-genomic viral RNA in nasopharyngeal swabs and oral swabs at Day 4 post-challenge in most animals, and reduced lung pathology relative to placebo-treated animals. Therapeutic administration of the casirivimab + imdevimab combination at 5 mg/kg and 50 mg/kg doses to hamsters 1-day post infection resulted in reduced weight loss relative to placebo treated animals, but had no clear effects on viral load in lung tissue. The applicability of these findings to a clinical setting is not known.

## **18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA**

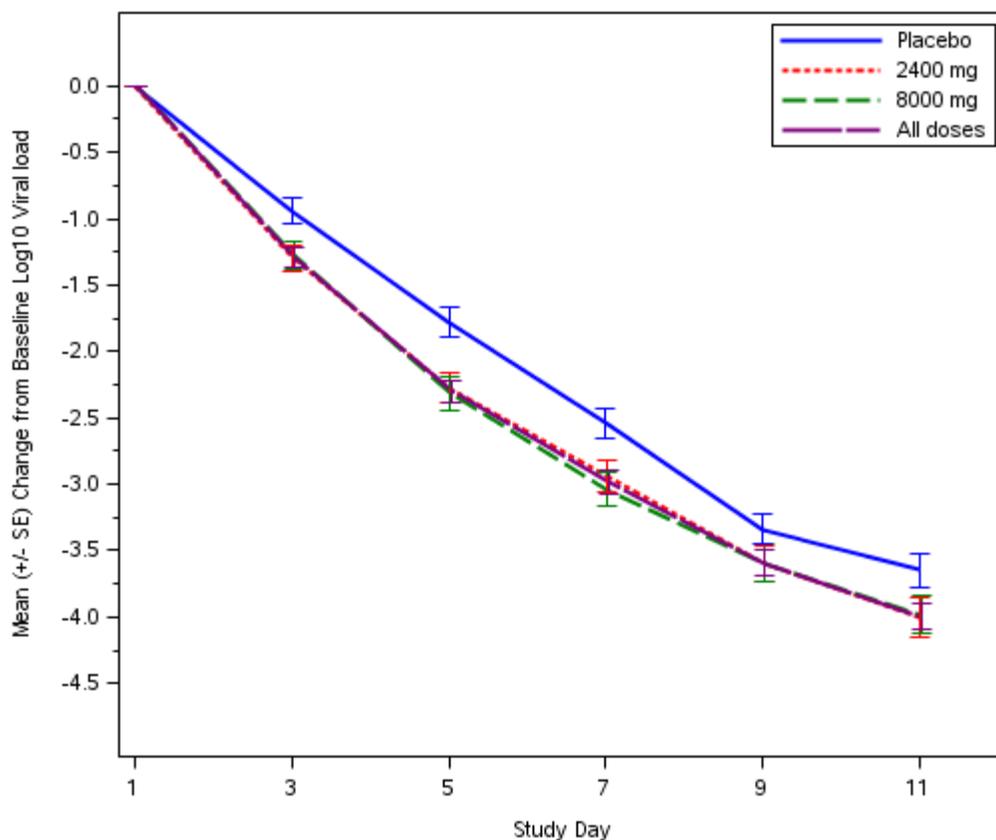
### **18.1 Mild to Moderate COVID-19 (R10933-10987-COV-2067)**

The data supporting this EUA are based on the analysis of Phase 1/2 from trial R10933-10987-COV-2067, that occurred after 799 enrolled subjects had completed at least 28 days of study duration. R10933-10987-COV-2067 is a randomized, double-blinded, placebo-controlled clinical trial studying casirivimab and imdevimab for the treatment of adult subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). The trial enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 viral infection determination. Subjects were randomized in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2,400 mg of casirivimab and imdevimab (1,200 mg of each) (n=266), or 8,000 mg of casirivimab and imdevimab (4,000 mg of each) (n=267), or placebo (n=266).

At baseline, the median age was 42 years (with 7% of subjects ages 65 years or older), 53% of the subjects were female, 85% were White, 50% were Hispanic or Latino, and 9% were Black; 34% were considered high risk (as defined in Section 2). Approximately 31% of subjects reported at least 1 severe symptom at baseline, 36% reported at least 1 moderate symptom and no severe symptoms, and 13% reported only mild symptoms. The median duration of symptoms was 3 days; mean viral load was 5.8  $\log_{10}$  copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The pre-specified primary endpoint in Phase 1/2 of trial R10933-10987-COV-2067 was the time weighted average (TWA) change from baseline in viral load ( $\log_{10}$  copies/mL), as measured by RT-qPCR in nasopharyngeal swab samples, in subjects with a positive baseline RT-qPCR value, i.e., the modified full analysis set (mFAS). In the mFAS (n=665) for the Phase 1/2 analysis, the difference in TWA from Day 1 through Day 7 for the pooled doses of casirivimab and imdevimab compared with placebo was -0.36  $\log_{10}$  copies/mL ( $p < 0.0001$ ). The largest reductions in viral load relative to placebo occurred in patients with high viral load (-0.78  $\log_{10}$  copies/mL) or who were seronegative (-0.69  $\log_{10}$  copies/mL) at baseline. Reductions occurring from Day 1 through Day 11 were similar to those for Day 1 through Day 7. **Figure 1** shows the mean change from baseline in SARS-COV-2 viral load over time.

**Figure 1. Mean Change from Baseline in SARS-COV-2 Viral Load Over Time**



While viral load was used to define the primary endpoint in the Phase 1/2 analysis, clinical evidence demonstrating that casirivimab and imdevimab may be effective came from the predefined secondary endpoint, medically attended visits (MAV) related to COVID-19. Medically attended visits comprised hospitalizations, emergency room visits, urgent care visits, or physician office/telemedicine visits for COVID-19. A lower proportion of subjects treated with casirivimab and imdevimab had COVID-19 related MAVs (2.8% for combined treatment arms vs 6.5% placebo). In post-hoc analyses, a lower proportion of subjects treated with casirivimab and imdevimab had COVID-19-related hospitalizations or emergency room visits compared to placebo, see [Table 3](#). Results for this endpoint were suggestive of a relatively flat dose-response relationship. The absolute risk reduction for casirivimab and imdevimab compared to placebo was greater in subjects at high risk for progression to severe COVID-19 and/or hospitalization, according to the criteria outlined in section 2 ([Table 4](#)).

**Table 3: Proportion of Subjects with Events of Hospitalization or Emergency Room Visits Within 28 Days After Treatment<sup>a</sup>**

Treatment	N <sup>b</sup>	Events	Proportion of subjects
Placebo	231	10	4%
2,400 mg <sup>c</sup> casirivimab and imdevimab	215	4	2%

8,000 mg <sup>d</sup> casirivimab and imdevimab	219	4	2%
All doses casirivimab and imdevimab	434	8	2%

<sup>a</sup> Hospitalization and emergency room visits were a subset of a key secondary endpoint, Medically-Attended Visits, which also included urgent care visits, physician's office visits and telemedicine visits.

<sup>b</sup> N = number of randomized subjects with a positive central-lab determined RT-qPCR from nasopharyngeal swab samples at randomization

<sup>c</sup> 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab)

<sup>d</sup> 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab)

**Table 4: Proportion of Subjects with Events of Hospitalization or Emergency Room Visits Within 28 Days After Treatment for Subjects at Higher Risk of Hospitalization<sup>a</sup>**

Treatment	N <sup>b</sup>	Events	Proportion of subjects
Placebo	78	7	9%
2,400 mg <sup>c</sup> casirivimab and imdevimab	70	2	3%
8,000 mg <sup>d</sup> casirivimab and imdevimab	81	2	2%
All doses casirivimab and imdevimab	151	4	3%

<sup>a</sup> Hospitalization and emergency room visits were a subset of a key secondary endpoint, Medically-Attended Visits, which also included urgent care visits, physician's office visits and telemedicine visits.

<sup>b</sup> N = number of randomized subjects with a positive central-lab determined RT-qPCR from nasopharyngeal swab samples at randomization

<sup>c</sup> 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab)

<sup>d</sup> 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab)

The median time to symptom improvement, as recorded in a trial-specific daily symptom diary, was 5 days for casirivimab and imdevimab-treated subjects, as compared with 6 days for placebo-treated subjects. Symptoms assessed were shortness of breath or difficulty breathing, chills, feverish, sore throat, cough, nausea, vomiting, diarrhea, headache, red or watery eyes, body and muscle aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomach ache, rash, sneezing, sputum/phlegm, runny nose. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent.

## 19 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

Casirivimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a single-dose vial. Refer to [Table 5](#).

Imdevimab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution supplied in a single-dose vial. Refer to [Table 5](#).

**CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER.**

**Table 5: How Casirivimab and Imdevimab are Supplied**

<b>Antibody</b>	<b>Concentration</b>	<b>Package Size</b>	<b>NDC Number</b>
<b>Casirivimab REGN 10933</b>	1332 mg/11.1 mL (120 mg/mL)	1 vial per pack	61755-024-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per pack	61755-026-01
<b>Imdevimab REGN10987</b>	1332 mg/11.1 mL (120 mg/mL)	1 vial per pack	61755-025-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per pack	61755-027-01

### **Storage and Handling**

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 administration. 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 and at room temperature up to 25°C (77°F) for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

## **20 PATIENT COUNSELING INFORMATION**

Patients treated with casirivimab and imdevimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines. Also see Fact Sheet for Patients, Parents and Caregivers.

## 21 CONTACT INFORMATION

For additional information visit [www.REGENCOV2.com](http://www.REGENCOV2.com)

If you have questions, please contact Regeneron at 1-844-734-6643.

### **REGENERON**

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

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Authorized: 11/2020

**FACT SHEET FOR PATIENTS, PARENTS AND CAREGIVERS  
EMERGENCY USE AUTHORIZATION (EUA) OF CASIRIVIMAB AND IMDEVIMAB FOR  
CORONAVIRUS DISEASE 2019  
(COVID-19)**

You are being given a medicine called **casirivimab** and **imdevimab** for the treatment of coronavirus disease 2019 (COVID-19). This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking casirivimab and imdevimab, which you may receive.

Receiving casirivimab and imdevimab may benefit certain people with COVID-19.

Read this Fact Sheet for information about casirivimab and imdevimab. Talk to your healthcare provider if you have questions. It is your choice to receive casirivimab and imdevimab or stop at any time.

**WHAT IS COVID-19?**

COVID-19 is caused by a virus called a coronavirus. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can occur and may cause some of your other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

**WHAT ARE THE SYMPTOMS OF COVID-19?**

The symptoms of COVID-19 include fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness including breathing problems can occur and may cause your other medical conditions to become worse.

**WHAT IS CASIRIVIMAB AND IMDEVIMAB?**

Casirivimab and imdevimab are investigational medicines used to treat mild to moderate symptoms of COVID-19 in non-hospitalized adults and adolescents (12 years of age and older who weigh at least 88 pounds (40 kg)), and who are at high risk for developing severe COVID-19 symptoms or the need for hospitalization. Casirivimab and imdevimab are investigational because they are still being studied. There is limited information known about the safety and effectiveness of using casirivimab and imdevimab to treat people with COVID-19.

The FDA has authorized the emergency use of casirivimab and imdevimab for the treatment of COVID-19 under an Emergency Use Authorization (EUA). For more information on EUA, see the **“What is an Emergency Use Authorization (EUA)?”** section at the end of this Fact Sheet.

**WHAT SHOULD I TELL MY HEALTH CARE PROVIDER BEFORE I RECEIVE CASIRIVIMAB AND IMDEVIMAB?**

**Tell your healthcare provider about all of your medical conditions, including if you:**

- Have any allergies

- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medications (prescription, over-the-counter, vitamins, and herbal products)

#### **HOW WILL I RECEIVE CASIRIVIMAB AND IMDEVIMAB?**

- Casirivimab and imdevimab are two investigational medicines given together as a single intravenous infusion (through a vein) for at least 1 hour.
- You will receive one dose of casirivimab and imdevimab by intravenous infusion.

#### **WHAT ARE THE IMPORTANT POSSIBLE SIDE EFFECTS OF CASIRIVIMAB AND IMDEVIMAB?**

Possible side effects of casirivimab and imdevimab are:

- Allergic reactions. Allergic reactions can happen during and after infusion with casirivimab and imdevimab. Tell your healthcare provider or nurse, or get medical help right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, low blood pressure, changes in your heartbeat, shortness of breath, wheezing, swelling of your lips, face, or throat, rash including hives, itching, headache, nausea, vomiting, sweating, muscle aches, dizziness and shivering.

The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

These are not all the possible side effects of casirivimab and imdevimab. Not a lot of people have been given casirivimab and imdevimab. Serious and unexpected side effects may happen. Casirivimab and imdevimab are still being studied so it is possible that all of the risks are not known at this time.

It is possible that casirivimab and imdevimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, casirivimab and imdevimab may reduce your body's immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

#### **WHAT OTHER TREATMENT CHOICES ARE THERE?**

Like casirivimab and imdevimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to <https://www.covid19treatmentguidelines.nih.gov/> for information on other medicines used to treat people with COVID-19.

It is your choice to be treated or not to be treated with casirivimab and imdevimab. Should you decide not to receive casirivimab and imdevimab or stop it at any time, it will not change your standard medical care.

#### **WHAT IF I AM PREGNANT OR BREASTFEEDING?**

There is limited experience treating pregnant women or breastfeeding mothers with casirivimab and imdevimab. For a mother and unborn baby, the benefit of receiving casirivimab and imdevimab may be

greater than the risk from the treatment. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

### **HOW DO I REPORT SIDE EFFECTS WITH CASIRIVIMAB AND IMDEVIMAB?**

Tell your healthcare provider right away if you have any side effect that bothers you or does not go away.

Report side effects to **FDA MedWatch** at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088 or call 1-844-734-6643.

### **HOW CAN I LEARN MORE?**

- Ask your health care provider.
- Visit [www.REGENCOV2.com](http://www.REGENCOV2.com)
- Visit <https://www.covid19treatmentguidelines.nih.gov/>
- Contact your local or state public health department.

### **WHAT IS AN EMERGENCY USE AUTHORIZATION (EUA)?**

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

Casirivimab and imdevimab have not undergone the same type of review as an FDA-approved or cleared product. The FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that the product meets certain criteria for safety, performance, and labeling and may be effective in treatment of patients during the COVID-19 pandemic. All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for casirivimab and imdevimab is in effect for the duration of the COVID-19 declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).

## **REGENERON**

Manufactured by:  
Regeneron Pharmaceuticals, Inc.  
777 Old Saw Mill River Road  
Tarrytown, NY 10591-6707

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Authorized: 11/2020

## CASIRIVIMAB AND IMDEVIMAB

Scan the QR code or go to [www.REGENCOV2.com](http://www.REGENCOV2.com) for the FDA-authorized Fact Sheet for detailed preparation and administration instructions for casirivimab and imdevimab.



**Casirivimab and imdevimab carton and vial labels may instead be labeled REGN10933 and REGN10987 respectively.**

Casirivimab and imdevimab may each be supplied as 1,332 mg/11.1 mL (120 mg/mL) single-dose vials OR 300 mg/2.5 mL (120 mg/mL) single-dose vials.

One 11.1 mL vial of one antibody and four 2.5 mL vials of the other antibody can be used to create one treatment course.

**CASIRIVIMAB AND IMDEVIMAB MUST BE ADMINISTERED TOGETHER  
AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.**

**You may receive cartons and vials of casirivimab and imdevimab that are labeled “for intravenous infusion or subcutaneous injection”. However, casirivimab and imdevimab MUST be administered by INTRAVENOUS (IV) INFUSION ONLY under this emergency use authorization.**

Casirivimab and imdevimab are not approved, but the U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products casirivimab and imdevimab to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization only for the duration of the declaration.

### LIMITATIONS OF AUTHORIZED USE

- Casirivimab and imdevimab are 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.
- Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19.

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to casirivimab and imdevimab. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions.

## IMPORTANT PRESCRIBING INFORMATION

<b>Subject: Preventing Medication Errors with Casirivimab and Imdevimab</b>
-----------------------------------------------------------------------------

Dear Healthcare Provider:

This notice is to make you aware of the correct route of administration of casirivimab and imdevimab. Although they are packaged separately, **casirivimab and imdevimab must be administered together after dilution by single intravenous (IV) infusion only.**

Casirivimab and imdevimab are authorized<sup>1</sup> for emergency use for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization. Healthcare Providers should administer casirivimab and imdevimab per the full Fact Sheet for Healthcare Providers available at [www.REGENCOV2.com](http://www.REGENCOV2.com).

**Casirivimab and Imdevimab Are Authorized ONLY for Intravenous Infusion after Dilution.**

You may receive cartons and vials of casirivimab and imdevimab that are labeled “for intravenous infusion or subcutaneous injection.” However, **casirivimab and imdevimab MUST be administered by INTRAVENOUS (IV) INFUSION ONLY** under this emergency use authorization. Healthcare providers should review the enclosed Fact Sheet for instructions on dosing, preparation and administration of casirivimab and imdevimab by intravenous infusion.

**Casirivimab and imdevimab must be administered together although they are packaged separately.**

There are three versions of casirivimab and imdevimab packaging, which are reproduced in the enclosure. Please note:

- Some cartons and vials of casirivimab and imdevimab may be instead labeled REGN10933 and REGN10987, respectively.
- Casirivimab and imdevimab may each be supplied as two different strengths: 1332 mg/11.1 mL single-dose vials and 300 mg/2.5 mL single-dose vials.
- One 11.1 mL vial of one antibody and four 2.5 mL vials of the other antibody can be used to create one treatment course.

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<sup>1</sup> Casirivimab and imdevimab are not approved, but The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products casirivimab and imdevimab to be administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization only for the duration of the declaration.

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**Regardless of the packaging, the 2 components, casirivimab and imdevimab, must be administered together as a single intravenous infusion. The route of administration authorized under the EUA is by intravenous infusion only after dilution.**

## **Healthcare Provider Action**

Healthcare providers should consider the following strategies in order to mitigate the risk of a possible medication error:

- Store casirivimab and imdevimab together in inventory.
- Create alerts in the electronic health record (EHR) systems for healthcare providers that casirivimab and imdevimab must be used together.
- Ensure that EHR systems always use casirivimab and imdevimab and only include an option for single IV infusion of casirivimab and imdevimab after dilution.

## **Reporting Adverse Events and Medication Errors**

Healthcare providers should direct questions about casirivimab and imdevimab packaging or use to the Regeneron Medical Information Department at 1-844-734-6643 or to [medical.information@regeneron.com](mailto:medical.information@regeneron.com).

Under the Emergency Use Authorization, adverse events must be reported within 7 calendar days from the onset of the event. MedWatch adverse event reports can be submitted to FDA online at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or by calling 1-800-FDA-1088.

- Complete and submit the report Online: [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm).
- Regular Mail or Fax: Download form <https://www.accessdata.fda.gov/scripts/medwatch/index.cfm> or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

Healthcare providers must report all serious adverse events and medication errors when utilizing casirivimab and imdevimab to Regeneron at [medical.information@regeneron.com](mailto:medical.information@regeneron.com).

The EUA Fact Sheet for Healthcare Providers is included with this notice, available at [www.REGENCOV2.com](http://www.REGENCOV2.com), or available by scanning the QR Code below:



Johnathan Lancaster, MD  
Vice President, Global Medical Affairs

# REGENERON

## Variations of the packaging and labeling of casirivimab and imdevimab

### 1a: casirivimab (also referred to as REGN10933) – 1332 mg/11.1 mL (120 mg/mL solution)

**Carton**

**Vial**

Contains 1 vial. Solution for intravenous administration. Administer in accordance with protocol instructions. Store refrigerated at 2°C – 8°C (36°F – 46°F) in the original carton to protect from light. Keep Out of Reach of Children, For Clinical Trial Use Only. Caution: New Drug – Limited by Federal (or United States) law to investigational use. Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 USA Tel: +1 914-847-7000

Subject Number \_\_\_\_\_  
Investigator \_\_\_\_\_  
Date Dispensed \_\_\_\_\_

### 1b: imdevimab (also referred to as REGN10987) – 1332 mg/11.1 mL (120 mg/mL solution)

**Carton**

**Vial**

Contains 1 vial. Solution for intravenous administration. Administer in accordance with protocol instructions. Store refrigerated at 2°C – 8°C (36°F – 46°F) in the original carton to protect from light. Keep Out of Reach of Children, For Clinical Trial Use Only. Caution: New Drug – Limited by Federal (or United States) law to investigational use. Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 USA Tel: +1 914-847-7000

Subject Number \_\_\_\_\_  
Investigator \_\_\_\_\_  
Date Dispensed \_\_\_\_\_

# REGENERON

## 2a: casirivimab (also referred to as REGN10933) – 300 mg/2.5 mL (120 mg/mL solution)

**Carton**

Subject Number \_\_\_\_\_  
Investigator \_\_\_\_\_  
Date Dispersed \_\_\_\_\_

Contains:  
1 vial Solution for intravenous infusion or subcutaneous injection  
Administer in accordance with protocol instructions.  
Store refrigerated at 2°C–8°C (36°F–46°F) in the original carton to protect from light.  
Keep Out of Reach of Children. For Clinical Trial Use Only.  
**Caution:** New Drug - Limited by Federal (or United States) law to investigational use.  
Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 USA  
Tel: +1 914-847-7000

Ref No. XXXXXXXX  
Lot XXXXXXXXXX  
**REGN10933**  
**300 mg/2.5 mL (120 mg/mL)**  
**MUST ADMINISTER WITH REGN10987**

Subject Number \_\_\_\_\_  
Investigator \_\_\_\_\_  
Date Dispersed \_\_\_\_\_

Contains:  
1 vial Solution for intravenous infusion or subcutaneous injection  
Administer in accordance with protocol instructions.  
Store refrigerated at 2°C–8°C (36°F–46°F) in the original carton to protect from light.  
Keep Out of Reach of Children. For Clinical Trial Use Only.  
**Caution:** New Drug - Limited by Federal (or United States) law to investigational use.  
Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 USA  
Tel: +1 914-847-7000

**Vial**



Subject Number \_\_\_\_\_  
Solution for intravenous infusion or subcutaneous injection.  
Administer in accordance with protocol instructions.  
Store refrigerated at 2°C–8°C (36°F–46°F)  
in original carton to protect from light.  
Keep Out of Reach of Children. For Clinical Trial Use Only.  
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701208

Lot

XXXXXXXXXX  
REGN10933  
300 MG/2.5ML  
(120 MG/ML)

## 2b: imdevimab (also referred to as REGN10987) – 300 mg/2.5 mL (120 mg/mL solution)

**Carton**

Subject Number \_\_\_\_\_  
Investigator \_\_\_\_\_  
Date Dispersed \_\_\_\_\_

Contains:  
1 vial Solution for intravenous infusion or subcutaneous injection  
Administer in accordance with protocol instructions.  
Store refrigerated at 2°C–8°C (36°F–46°F) in the original carton to protect from light.  
Keep Out of Reach of Children. For Clinical Trial Use Only.  
**Caution:** New Drug - Limited by Federal (or United States) law to investigational use.  
Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 USA  
Tel: +1 914-847-7000

Ref No. XXXXXXXX  
Lot XXXXXXXXXX  
**REGN10987**  
**300 mg/2.5 mL (120 mg/mL)**  
**MUST ADMINISTER WITH REGN10933**

Subject Number \_\_\_\_\_  
Investigator \_\_\_\_\_  
Date Dispersed \_\_\_\_\_

Contains:  
1 vial Solution for intravenous infusion or subcutaneous injection  
Administer in accordance with protocol instructions.  
Store refrigerated at 2°C–8°C (36°F–46°F) in the original carton to protect from light.  
Keep Out of Reach of Children. For Clinical Trial Use Only.  
**Caution:** New Drug - Limited by Federal (or United States) law to investigational use.  
Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 USA  
Tel: +1 914-847-7000

**Vial**



Subject Number \_\_\_\_\_  
Solution for intravenous infusion or subcutaneous injection.  
Administer in accordance with protocol instructions.  
Store refrigerated at 2°C–8°C (36°F–46°F)  
in original carton to protect from light.  
Keep Out of Reach of Children. For Clinical Trial Use Only.  
**Caution:** New Drug - Limited by Federal (or United States) law to investigational use. Regeneron Pharmaceuticals, Inc. Tarrytown, NY 10591 USA Tel: +1 914-847-7000

701208

Lot

XXXXXXXXXX  
REGN10987  
300 MG/2.5ML  
(120 MG/ML)

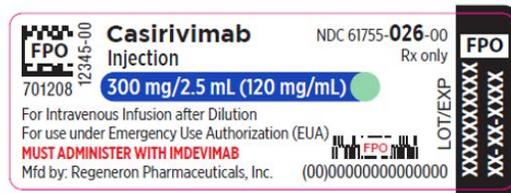
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## 3a: casirivimab (also referred to as REGN10933) – 300 mg/2.5 mL (120 mg/mL solution)

Carton



Vial

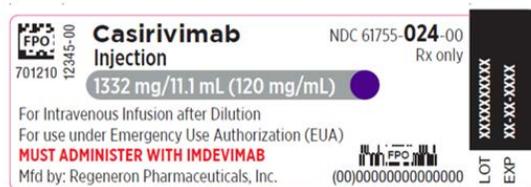


## 3b: casirivimab (also referred to as REGN10933) – 1332 mg/11.1 mL (120 mg/mL solution)

Carton

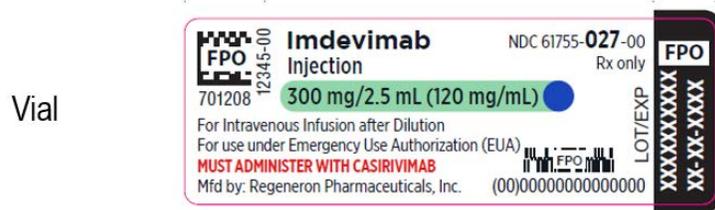


Vial

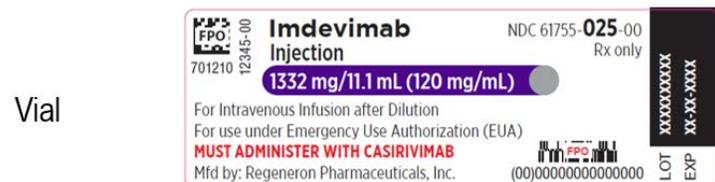


# REGENERON

3c: imdevimab (also referred to as REGN10987) – 300 mg/2.5 mL (120 mg/mL solution)



3d: imdevimab (also referred to as REGN10987) – 1332 mg/11.1 mL (120 mg/mL solution)



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JOHN J FARLEY  
11/21/2020 03:56:20 PM

**US FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF INFECTIOUS DISEASES  
DIVISION OF ANTIVIRALS  
ADDENDUM TO EUA SCIENTIFIC REVIEW**

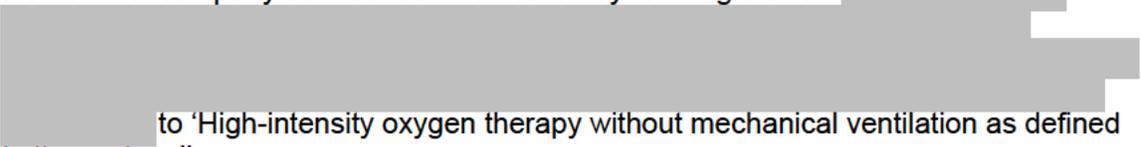
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**EUA:** 000091  
**Product:** Casirivimab (REGN10933) and imdevimab (REGN10987)  
**Applicant:** Regeneron Pharmaceuticals, Inc.  
**Intended Use:** Mild to moderate coronavirus disease 2019 (COVID-19)  
**Intended Population:** Adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral test and who are at high risk for progressing to severe COVID-19 and/or hospitalization

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This addendum summarizes the corrections made to the scientific review for EUA 91 issued on November 21, 2020. The corrections to the scientific review do not alter the efficacy and safety conclusion that resulted in issuance of EUA 91. The corrections to the scientific review do not alter the information in the approved EUA Healthcare Provider and Patient Fact Sheets.

The corrections are as follows:

- 1) Minor editorial change from 'COV' to 'HV' in study title.
- 2) Removal of company confidential information by revising the text (b) (4)  
 to 'High-intensity oxygen therapy without mechanical ventilation as defined in the protocol'.
- 3) Removal of Figure 1 as time weighted average change from baseline endpoint is a cumulative endpoint and plotting cumulative data over time is not appropriate.
- 4) Revision of text 'The Applicant conducted subgroup analyses which...' to 'The Applicant prespecified to test hierarchically reduction in viral load in certain subgroups. These showed a greater magnitude...'
- 5) Removal of text 'It should be noted that some of these MAV events were telemedicine events for relatively minor symptoms and were not necessarily representative of clinically important disease progression' as it is not accurate given the limited information available.
- 6) Revision of '...relying on post-hoc analysis of the prespecified endpoint of medically attended visits...' to 'relying on post-hoc analysis of the prespecified endpoint of medically attended visits in the subgroup of subjects who were at higher risk of hospitalization ....'
- 7) Revision of 'phase 1' to 'phase 1 and 2'.
- 8) Revision of 'method, known to be associated with low...' to '...method, known to generally have more issues of sensitivity and interference'.

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