FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF REGEN-COV™ (casirivimab with 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 product, REGEN-COV (casirivimab with 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.

RECENT MAJOR CHANGES

- Antiviral Resistance (Box and Section 15): addition of information on susceptibility of SARS-CoV-2 variants to REGEN-COV (Table 3) Revised 3/2021
- Dose Preparation and Administration Instructions (Section 2.4): provides updated minimum infusion times based on size of infusion bag used Revised 03/2021
- New proprietary name: REGEN-COV Revised 02/2021
- Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1) – addition of new symptoms Revised 02/2021
- Warnings: Clinical Worsening After REGEN-COV Administration (Section 5.2) – new warning added Revised 02/2021

LIMITATIONS OF AUTHORIZED USE

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

REGEN-COV has been authorized by FDA for the emergency uses described above.

REGEN-COV is not FDA-approved for these uses.

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

Each REGEN-COV dose pack contains sufficient number of vials of casirivimab (REGN10933) and imdevimab (REGN10987) to prepare one treatment dose *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)]*. Casirivimab and **imdevimab** vial labels and carton labeling may instead be labeled **REGN10933** and **REGN10987,** respectively.

This EUA is for the use of the unapproved product, REGEN-COV (casirivimab with 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) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥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, 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.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health care providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

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

REGEN-COV 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 REGEN-COV. 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 a 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 with 1,200 mg of imdevimab together as a single IV infusion via pump or gravity (see Table 1).
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.
- Patients treated with REGEN-COV 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 REGEN-COV in COVID-19, please see www.clinicaltrials.gov.

Contraindications

None.

Dosing

CASIRIVIMAB WITH 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 product REGEN-COV (casirivimab with 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) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥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, 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 via pump or gravity (see Table 1).

Casirivimab and imdevimab solutions must be diluted prior to administration.

Casirivimab and imdevimab should be given together as soon as possible after positive SARS-CoV-2 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 with 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 a prefilled IV infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection.
4. Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial using two separate syringes (see Table 1) and inject all 20 mL into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see Table 1). Discard any product remaining in the vial.
5. Gently invert infusion bag by hand approximately 10 times to mix. **Do not shake**.
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.
    - If immediate administration is not possible, store the diluted casirivimab with imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Each REGEN-COV dose pack contains sufficient number of vials of casirivimab (REGN10933) and imdevimab (REGN10987) to prepare one treatment dose *[see Full EUA Prescribing Information, How Supplied/Storage and Handling (19)]*. Casirivimab and **imdevimab** vial labels and carton labeling may instead be labeled **REGN10933** and **REGN10987,** respectively.

Table 1: Recommended Dosing, Dilution and Administration Instructions for Casirivimab with Imdevimab for IV Infusion

Casirivimab with Imdevimab 2,400 mg Dose[a]. Add: • **10 mL of casirivimab (use 1 vial of 11.1 mL OR 4 vials of 2.5 mL) and** • **10 mL of imdevimab (use 1 vial of 11.1 mL OR 4 vials of 2.5 mL)** **for a total of 20 mL into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below[b]**		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL[c]	210 mL/hr	20 minutes
100 mL	310 mL/hr	23 minutes
150 mL	310 mL/hr	33 minutes
250 mL	310 mL/hr	52 minutes

[a] 1,200 mg casirivimab and 1,200 mg imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.
[b] After infusion is complete, flush with 0.9% Sodium Chloride Injection
[c] The minimum infusion time for patients administered casirivimab with imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride infusion bag must be at least 20 minutes to ensure safe use.

Administration

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

- Gather the recommended materials for infusion:
    - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
    - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the IV bag.

- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see Table 1). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush the tubing with 0.9% Sodium Chloride Injection to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

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 REGEN-COV (casirivimab with imdevimab). Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of REGEN-COV (casirivimab with 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 REGEN-COV. These reactions may be severe or life-threatening.

Signs and symptoms of infusion-related reactions may include:

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

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

Clinical Worsening After REGEN-COV Administration

Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status.

Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

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

Benefit of treatment with REGEN-COV (casirivimab with imdevimab) has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, REGEN-COV is 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 REGEN-COV (casirivimab with imdevimab) [*see Full EUA Prescribing Information, Clinical Trials Experience (6.1)*].

Additional adverse events associated with REGEN-COV, 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 REGEN-COV (casirivimab with imdevimab), including:

- FDA has authorized the emergency use of REGEN-COV (casirivimab with 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 REGEN-COV.
- The significant known and potential risks and benefits of REGEN-COV, 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 REGEN-COV 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 REGEN-COV related to COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR REGEN-COV UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this unapproved product under EUA and to optimize the potential benefit of REGEN-COV (casirivimab with imdevimab to be administered together), the following items are required. Use of REGEN-COV 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 REGEN-COV. 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 REGEN-COV, and
    c. Informed that REGEN-COV is an unapproved drug that is authorized for use under this Emergency Use Authorization.
3. Patients with known hypersensitivity to any ingredient of REGEN-COV must not receive REGEN-COV.
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 REGEN-COV.
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 REGEN-COV treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "REGEN-COV use for COVID-19 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, 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 "REGEN-COV use for COVID-19 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
    - Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

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

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to REGEN-COV (casirivimab with 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 product REGEN-COV (casirivimab with 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.[1] As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

[1] 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 REGEN-COV (casirivimab with 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 REGEN-COV 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.REGENCOV.com
If you have questions, please contact Regeneron at 1-844-734-6643.

END SHORT VERSION FACT SHEET
Long Version Begins on Next Page

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

1 AUTHORIZED USE

REGEN-COV (casirivimab with imdevimab to be administered together) is authorized 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

- REGEN-COV (casirivimab with imdevimab) is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with REGEN-COV has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[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 WITH 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 product REGEN-COV (casirivimab with 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) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥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, 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 via pump or gravity (see Table 1). Casirivimab and imdevimab solutions must be diluted prior to administration.

Casirivimab with imdevimab should be given together 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. REGEN-COV (casirivimab with imdevimab) is 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.
3. Obtain a prefilled IV infusion bag containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection.
4. Withdraw 10 mL of casirivimab and 10 mL of imdevimab from each respective vial using two separate syringes (see Table 1) and inject all 20 mL into a prefilled infusion bag containing 0.9% Sodium Chloride Injection (see Table 1). Discard any product remaining in the vial.
5. Gently invert infusion bag by hand approximately 10 times. **Do not shake.**
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.

- If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 1: Recommended Dosing, Dilution and Administration Instructions for Casirivimab with Imdevimab for IV Infusion

Casirivimab with Imdevimab 2,400 mg Dose[a]. Add: • **10 mL of casirivimab (use 1 vial of 11.1 mL OR 4 vials of 2.5 mL) and** • **10 mL of imdevimab (use 1 vial of 11.1 mL OR 4 vials of 2.5 mL)** **for a total of 20 mL into a prefilled 0.9% sodium chloride infusion bag and administer as instructed below[b]**		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL[c]	210 mL/hr	20 minutes
100 mL	310 mL/hr	23 minutes
150 mL	310 mL/hr	33 minutes
250 mL	310 mL/hr	52 minutes

[a] 1,200 mg casirivimab and 1,200 mg imdevimab are added to the same infusion bag and administered together as a single intravenous infusion.
[b] After infusion is complete, flush with 0.9% Sodium Chloride Injection.
[c] The minimum infusion time for patients administered casirivimab with imdevimab together using the 50 mL prefilled 0.9% Sodium Chloride infusion bag must be at least 20 minutes to ensure safe use.

Administration

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

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 micron polyethersulfone (PES) filter
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter (see Table 1). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.

- After infusion is complete, **flush the tubing** with 0.9% Sodium Chloride Injection to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

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

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

Each REGEN-COV dose pack contains sufficient number of vials of casirivimab (REGN10933) and imdevimab (REGN10987) to prepare one treatment dose *[see How Supplied/Storage and Handling (19)]*. Casirivimab and **imdevimab** vial labels and carton labeling may instead be labeled **REGN10933** and **REGN10987,** respectively.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

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

5.1 Hypersensitivity including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of REGEN-COV (casirivimab with 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 REGEN-COV. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include:

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

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

5.2 Clinical Worsening After REGEN-COV Administration

Clinical worsening of COVID-19 after administration of REGEN-COV has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to REGEN-COV use or were due to progression of COVID-19.

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

Benefit of treatment with REGEN-COV (casirivimab with imdevimab) has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as REGEN-COV, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, REGEN-COV is 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 REGEN-COV (casirivimab with imdevimab) in clinical trials in both hospitalized and non-hospitalized patients.

6.1 Clinical Trials Experience

The safety of REGEN-COV (casirivimab with 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=260), or placebo (n=262). The adverse events collected were infusion-related reactions and hypersensitivity reactions of moderate severity or higher through day 29, all serious adverse events (SAEs); and in phase 1 only, all grade 3 and 4 treatment-emergent adverse events.

Serious adverse events were reported in 4 subjects (1.6%) in the REGEN-COV 2,400 mg group, 2 subjects (0.8%) in the REGEN-COV 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 REGEN-COV), intestinal obstruction and dyspnea (8,000 mg REGEN-COV) and COVID-19, pneumonia and hypoxia (placebo). REGEN-COV is 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 REGEN-COV (casirivimab with 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 REGEN-COV (casirivimab with imdevimab) are ongoing *[see Overall Safety Summary (6)]*.

Completion of FDA MedWatch Form to report all medication errors and serious adverse events* occurring during REGEN-COV use and considered to be potentially related to REGEN-COV 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 REGEN-COV, 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, 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 REGEN-COV
- 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 "REGEN-COV use for COVID-19 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

Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

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

10 DRUG INTERACTIONS

REGEN-COV consists of 2 monoclonal antibodies (mAbs), casirivimab and imdevimab, 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. REGEN-COV (casirivimab with 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 Lactation

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 REGEN-COV (casirivimab with imdevimab) and any potential adverse effects on the breastfed child from REGEN-COV 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 with imdevimab have not been assessed in pediatric patients. The recommended dosing regimen is expected to result in comparable serum exposures of casirivimab with 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 REGEN-COV (casirivimab with 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 (IgG1κ) and imdevimab (IgG1λ) 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 casirivimab and imdevimab together 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 REGEN-COV (casirivimab with 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 REGEN-COV 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 casirivimab and imdevimab together neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} 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 casirivimab and imdevimab together mediated ADCC with human natural killer (NK) effector cells. Casirivimab, imdevimab and casirivimab and imdevimab together mediated ADCP with human macrophages. Casirivimab, imdevimab and casirivimab and imdevimab together 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_{50} values. Casirivimab and imdevimab together and imdevimab alone, but not casirivimab alone, mediated entry of pseudoparticles into $Fc\gamma R2^+$ Raji and $Fc\gamma R1^+/Fc\gamma R2^+$ THP1 cells (maximum infection in total cells of 1.34% and 0.24%, respectively, for imdevimab; 0.69% and 0.06%, respectively for casirivimab and imdevimab together), 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 casirivimab and imdevimab administered together. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

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

which showed reduced susceptibility to imdevimab alone included substitutions K444N (>755-fold), K444Q (>548-fold), K444T (>1,033-fold), and V445A (548-fold). Casirivimab and imdevimab together showed reduced susceptibility to variants with K444T (6-fold) and V445A (5-fold) substitutions.

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

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

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

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

[a] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.
[b] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.
[c] No change: <2-fold reduction in susceptibility.
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

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

In clinical trial R10933-10987-COV-2067, interim data indicated only one variant (G446V) occurring at an allele fraction ≥15%, which was detected in 3/66 subjects who had nucleotide sequencing data, each at a single time point (two at baseline in subjects from placebo and 2,400 mg casirivimab and imdevimab groups, and one at Day 25 in a subject from the 8,000 mg

casirivimab and imdevimab group). The G446V variant had reduced susceptibility to imdevimab of 135-fold compared to wild-type in a VSV pseudoparticle neutralization assay but retained susceptibility to casirivimab alone and casirivimab and imdevimab together.

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

Immune Response Attenuation

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

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

Casirivimab and imdevimab administered together has been assessed in rhesus macaque and Syrian golden hamster treatment models of SARS-CoV-2 infection. Therapeutic administration of casirivimab and imdevimab together 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 $\log_{10}$ 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 casirivimab and imdevimab together 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)

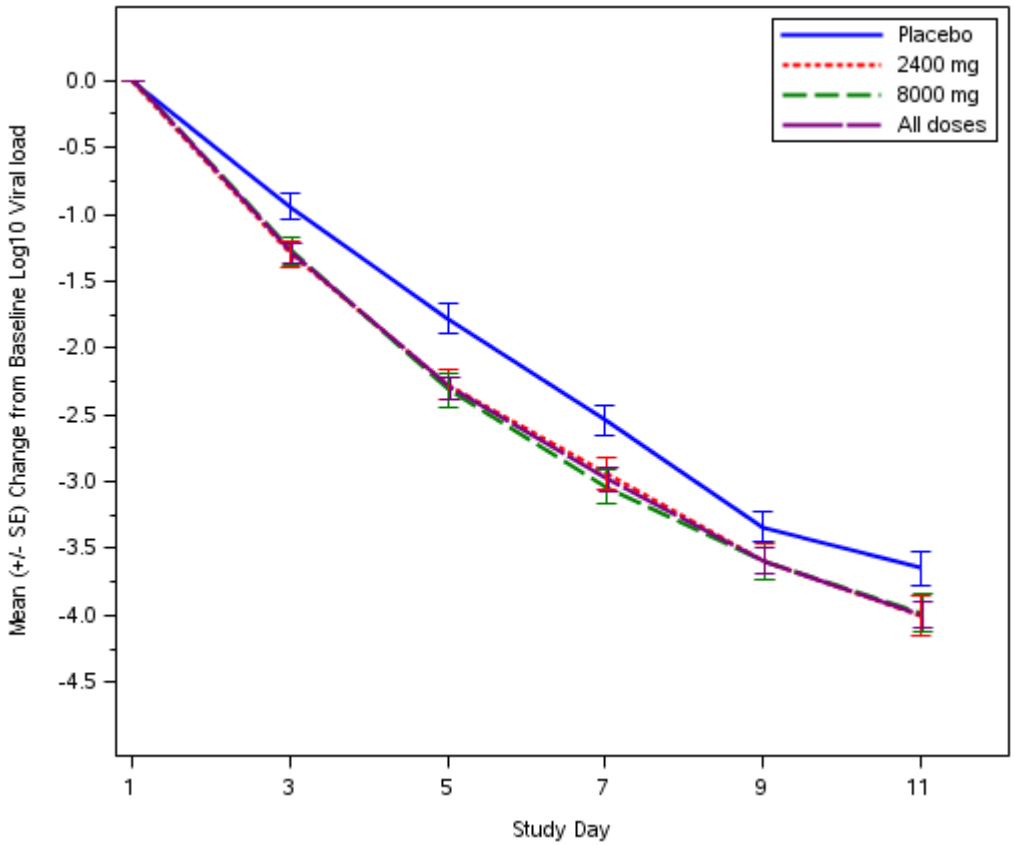
The data supporting this EUA are based on the analysis of Phase 1/2 from trial R10933-10987-COV-2067, that occurred after 799 enrolled subjects had completed at least 28 days of study duration. R10933-10987-COV-2067 is a randomized, double-blinded,

placebo-controlled clinical trial studying REGEN-COV (casirivimab with imdevimab) for the treatment of adult subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). The trial enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 viral infection determination. Subjects were randomized in a 1:1:1 manner to receive a single intravenous (IV) infusion of 2,400 mg of REGEN-COV (1,200 mg of casirivimab and 1,200 mg of imdevimab) (n=266), or 8,000 mg of REGEN-COV (4,000 mg of casirivimab and 4,000 mg of imdevimab) (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 REGEN-COV 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 for the Phase 1/2 analysis, the difference in TWA from Day 1 through Day 7 for the pooled doses of REGEN-COV compared with placebo (n=665) 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 REGEN-COV 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 REGEN-COV 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 REGEN-COV 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 REGEN-COV 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[a]

Treatment	N[b]	Events	Proportion of subjects
Placebo	231	10	4%
2,400 mg[c] REGEN-COV	215	4	2%
8,000 mg[d] REGEN-COV	219	4	2%

All doses REGEN-COV	434	8	2%

[a] 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.
[b] N = number of randomized subjects with a positive central-lab determined RT-qPCR from nasopharyngeal swab samples at randomization
[c] 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab)
[d] 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[a]

Treatment	N[b]	Events	Proportion of subjects
Placebo	78	7	9%
2,400 mg[c] REGEN-COV	70	2	3%
8,000 mg[d] REGEN-COV	81	2	2%
All doses REGEN-COV	151	4	3%

[a] 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.
[b] N = number of randomized subjects with a positive central-lab determined RT-qPCR from nasopharyngeal swab samples at randomization
[c] 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab)
[d] 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 REGEN-COV-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: Individual Package Size

Antibody	Concentration	Package Size	NDC Number
Casirivimab REGN10933	1332 mg/11.1 mL (120 mg/mL)	1 vial per carton	61755-024-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per carton	61755-026-01
Imdevimab REGN10987	1332 mg/11.1 mL (120 mg/mL)	1 vial per carton	61755-025-01
	300 mg/2.5 mL (120 mg/mL)	1 vial per carton	61755-027-01

Each REGEN-COV dose pack contains sufficient number of vials of casirivimab (REGN10933) and imdevimab (REGN10987) to prepare one treatment dose. Refer to Table 6.

Table 6: Dose Pack Providing 1 Treatment Dose of 2,400 mg (1,200 mg Casirivimab and 1,200 mg Imdevimab)

Dose-Pack Size	Dose-Pack Components	Concentration	Dose-Pack NDC Number
2 Cartons	**1 casirivimab REGN10933** (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-035-02
	1 imdevimab REGN10987 (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	
8 Cartons	**4 casirivimab REGN10933** (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-036-08
	4 imdevimab REGN10987 (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
5 Cartons	**1 casirivimab REGN10933** (NDC 61755-024-01)	1,332 mg/11.1 mL (120 mg/mL)	61755-037-05
	4 imdevimab REGN10987 (NDC 61755-027-01)	300 mg/2.5 mL (120 mg/mL)	
5 Cartons	**4 casirivimab REGN10933** (NDC 61755-026-01)	300 mg/2.5 mL (120 mg/mL)	61755-038-05
	1 imdevimab REGN10987 (NDC 61755-025-01)	1,332 mg/11.1 mL (120 mg/mL)	

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

20 PATIENT COUNSELING INFORMATION

Patients treated with REGEN-COV (casirivimab with 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.REGENCOV.com
If you have questions, please contact Regeneron at 1-844-734-6643.

REGENERON

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