# NIH COVID-19 Treatment Guidelines Strongly Recommend Use of REGEN-COV™ (casirivimab with imdevimab) in Outpatients at High Risk of Clinical Progression

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**Some panel members also recommended preferential use of REGEN-COV antibody cocktail in regions where certain variants are common**

TARRYTOWN, N.Y., April 9, 2021 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) announced today that newly updated National Institutes of Health (NIH) COVID-19 Treatment Guidelines strongly recommend that REGEN-COV™ (casirivimab with imdevimab) be used in non-hospitalized COVID-19 patients ("outpatients") at high risk of clinical progression. The Category 'AIIa' is a 'strong' rating based on results of randomized trials.

The recommendation from the NIH COVID-19 Treatments Guidelines Panel is a critical step in helping make monoclonal antibody therapies like REGEN-COV available for all appropriate patients in the U.S. The new guidelines are based in part on robust clinical data involving more than 4,500 outpatients showing that REGEN-COV significantly reduced the risk of hospitalization or death by 70% compared to placebo.

"With these clear new NIH guidelines, Emergency Use Authorization from the U.S. Food and Drug Administration, ample supply of REGEN-COV, and the medicine being supplied free of charge by the U.S. government, the time for equivocation has passed — we must now all do whatever it takes to make sure appropriate patients are treated as early as possible after diagnosis," said Leonard S. Schleifer, M.D., Ph.D., President and CEO at Regeneron. "If we work together, we can avoid tens of thousands of needless hospitalizations or deaths from COVID-19. We will also continue to partner with stakeholders to address other key bottlenecks such as education, ease of administration and better systems to ensure infusion reimbursement."

Despite the strong progress being made with vaccination, in the U.S. approximately 2 million people a month are still diagnosed with COVID-19 and tens of thousands are at risk of dying from COVID-19.

Importantly, some NIH panel members recommended REGEN-COV as the preferred antibody cocktail for COVID-19 in areas where variants are common, given REGEN-COV's continued potency *in vitro* against the variants first identified in the United Kingdom, Brazil, South Africa, New York and California, while acknowledging that it is not known whether *in vitro* susceptibility data correlates with clinical outcomes. The U.S. Food and Drug Administration (FDA) recently authorized updated Emergency Use Authorization (EUA) fact sheets for all authorized monoclonal antibody treatments, which indicate that REGEN-COV is the only therapy to retain potency against these key emerging variants. In many parts of the U.S., variants now make up the majority of all new COVID-19 cases.

"Regeneron continues to innovate to respond to this devastating pandemic. With approximately 60,000 new infections daily, many of them in high-risk individuals, it's clear there is an urgent need to improve access to treatments like REGEN-COV that are proven to reduce hospitalization or death," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "In addition to working to advance simpler subcutaneous administration of REGEN-COV, we look forward to sharing additional data soon on the use of REGEN-COV to prevent infection."

Although REGEN-COV is not currently recommended for people hospitalized due to COVID-19, the panel recommended that REGEN-COV use should be considered for persons with mild-to-moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

The development and manufacturing of REGEN-COV have been funded in part with federal funds from the Biomedical Advanced Research and Development Authority (BARDA), part of the U.S. Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, under OT number: HHSO100201700020C.

**About the REGEN-COV Antibody Cocktail**

REGEN-COV (casirivimab with imdevimab) is a cocktail of two monoclonal antibodies (also known as REGN10933 and REGN10987) that was designed specifically to block infectivity of SARS-CoV-2, the virus that causes COVID-19, using Regeneron's proprietary *VelocImmune*® and *VelociSuite*® technologies. The two potent, virus-neutralizing antibodies that form the cocktail bind non-competitively to the critical receptor binding domain of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population, as detailed in *Science*.

Under an EUA issued by the FDA, REGEN-COV is currently available in the U.S. to treat mild-to-moderate COVID-19 in adults, as well as in pediatric patients at least 12 years of age and weighing at least 40 kg, who have received positive results of direct SARS-CoV-2 viral testing and are at high risk for progressing to severe COVID-19 and/or hospitalization. REGEN-COV has not been approved by FDA but has been authorized for emergency use. This use is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

REGEN-COV is currently authorized and available in a 2,400 mg IV dose, with infusion times as short as 20 minutes. The criteria for 'high-risk' patients are described in the Fact Sheet for Healthcare Providers. In the U.S., REGEN-COV is not authorized for use in patients who are hospitalized due to COVID-19 or require oxygen therapy, or for people currently using chronic oxygen therapy because of an underlying comorbidity who require an increase in baseline oxygen flow rate due to COVID-19.

Under this EUA, REGEN-COV is available throughout the U.S. – information on availability in your area is available from the Department of Health and Human Services and the National Infusion Center Association.

Regeneron is collaborating with Roche to increase global supply of REGEN-COV. Regeneron is responsible for development and distribution of the treatment in the U.S., and Roche is primarily responsible for development and distribution outside the U.S. The companies share a commitment to making the antibody cocktail available to COVID-19 patients around the globe and will support access in low- and lower-middle-income countries through drug donations to be made in partnership with public health organizations.

**About Regeneron's *VelocImmune* Technology**

Regeneron's *VelocImmune* technology utilizes a proprietary genetically engineered mouse platform endowed with a genetically humanized immune system to produce optimized fully human antibodies. When Regeneron's co-Founder, President and Chief Scientific Officer George D. Yancopoulos was a graduate student with his mentor Frederick W. Alt in 1985, they were the first to envision making such a genetically humanized mouse, and Regeneron has spent decades inventing and developing *VelocImmune* and related *VelociSuite* technologies. Dr. Yancopoulos and his team have used *VelocImmune* technology to create approximately a quarter of all original, FDA-approved fully human monoclonal antibodies currently available. This includes REGEN-COV™ (casirivimab with imdevimab), Dupixent® (dupilumab), Libtayo® (cemiplimab-rwlc), Praluent® (alirocumab), Kevzara® (sarilumab), Evkeeza™ (evinacumab-dgnb) and Inmazeb™ (atoltivimab, maftivimab and odesivimab-ebgn).

**AUTHORIZED USE AND IMPORTANT SAFETY INFORMATION**

**Authorized Emergency Use**

REGEN-COV, (casirivimab with imdevimab to be administered together) is authorized 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. [see Limitations of Authorized Use]

- REGEN-COV has not been approved, but has been authorized for emergency use by FDA
- This use is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner
- Healthcare providers should review the **Fact Sheet for Healthcare Providers** for information on the authorized use of REGEN-COV and mandatory requirements of the EUA and must comply with the requirements of the EUA. The **FDA Letter of Authorization** is available for reference**,** as well as the **Dear Healthcare Provider Letter** and **Patient Fact Sheet**

**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.

**Definition of High-Risk Patients**

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 (e.g., 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. Healthcare providers should review the Antiviral Resistance information in Section 15 of the Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant-cases.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.

**IMPORTANT SAFETY INFORMATION**
REGEN-COV (casirivimab with imdevimab) is an unapproved investigational therapy, and there are limited clinical data available. Serious and unexpected adverse events may occur that have not been previously reported with REGEN-COV use.

**Warnings and Precautions:**

- **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions:** There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of REGEN-COV. 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.
    - **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.
- **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 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 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.

**Adverse Reactions:**

- Serious adverse events (SAEs) were reported in 4 (1.6%) patients in REGEN-COV 2,400 mg group, 2 (0.8%) patients in REGEN-COV 8,000 mg group and 6 (2.3%) patients 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).**
- 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, 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.

**Patient Monitoring Recommendations**: Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

**Use in Specific Populations:**

- **Pregnancy:** There is currently limited clinical experience in the use of REGEN-COV in COVID-19 patients who are pregnant. REGEN-COV therapy should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.
- **Lactation:** There is currently no clinical experience in use of REGEN-COV in COVID-19 patients who are breastfeeding. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REGEN-COV and any potential adverse effects on the breastfed child from REGEN-COV or from the underlying maternal condition.

**About Regeneron**
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded

and led for over 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to nine FDA-approved treatments and numerous product candidates in development, almost all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, pain, hematology, infectious diseases and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*®, which uses unique genetically humanized mice to produce optimized fully human antibodies and bispecific antibodies, and through ambitious research initiatives such as the Regeneron Genetics Center, which is conducting one of the largest genetics sequencing efforts in the world. For additional information about the company, please visit www.regeneron.com or follow @Regeneron on Twitter.

**Regeneron Forward-Looking Statements and Use of Digital Media**

**Forward-Looking Statements and Use of Digital Media**

*This press release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the impact of SARS-CoV-2 (the virus that has caused the COVID-19 pandemic) on Regeneron's business and its employees, collaborators, and suppliers and other third parties on which Regeneron relies, Regeneron's and its collaborators' ability to continue to conduct research and clinical programs, Regeneron's ability to manage its supply chain, net product sales of products marketed or otherwise commercialized by Regeneron and/or its collaborators (collectively, "Regeneron's Products"), and the global economy; the nature, timing, and possible success and therapeutic applications of Regeneron's Products and product candidates and research and clinical programs now underway or planned, including the development program relating to REGEN-COV™ (casirivimab with imdevimab) antibody cocktail; how long the Emergency Use Authorization ("EUA") granted by the U.S. Food and Drug Administration (the "FDA") for REGEN-COV will remain in effect and whether the EUA is revoked by the FDA based on its determination that the underlying health emergency no longer exists or warrants such authorization or other reasons; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's product candidates (including REGEN-COV) and new indications for Regeneron's Products; whether subcutaneous administration of REGEN-COV will be included in the EUA for REGEN-COV based on previously reported data or otherwise; uncertainty of the utilization rate, market acceptance, or commercial success of Regeneron's Products and product candidates (including REGEN-COV); the impact of recommendations, guidelines (including the National Institutes of Health COVID-19 Treatment Guidelines discussed in this press release), or studies (whether conducted by Regeneron or others and whether mandated or voluntary) on any potential regulatory approval and/or the utilization rate, market acceptance, or commercial success of Regeneron's Products and product candidates (such as REGEN-COV); the ability of Regeneron's collaborators, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and product candidates (including REGEN-COV) and the impact of the foregoing on Regeneron's ability to supply its Products and product candidates (including REGEN-COV); the ability of Regeneron to manage supply chains for multiple products and product candidates; safety issues resulting from the administration of Regeneron's Products and product candidates (such as REGEN-COV) in patients, including serious complications or side effects in connection with the use of Regeneron's Products and product candidates in clinical trials; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's Products and product candidates, including REGEN-COV; ongoing regulatory obligations and oversight impacting Regeneron's Products, research and clinical programs, and business, including those relating to patient privacy; the availability and extent of reimbursement of Regeneron's Products from third-party payers, including private payer healthcare and insurance programs, health maintenance organizations, pharmacy benefit management companies, and government programs such as Medicare and Medicaid; coverage and reimbursement determinations by such payers and new policies and procedures adopted by such payers; competing drugs and product candidates that may be superior to, or more cost effective than, Regeneron's Products and product candidates; the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license, collaboration, or supply agreement, including Regeneron's agreements with Sanofi, Bayer, and Teva Pharmaceutical Industries Ltd. (or their respective affiliated companies, as applicable), as well as Regeneron's collaboration with Roche relating to REGEN-COV, to be cancelled or terminated; and risks associated with intellectual property of other parties and pending or future litigation relating thereto (including the patent litigation and other related proceedings relating to EYLEA® (aflibercept) Injection, Dupixent® (dupilumab), Praluent® (alirocumab), and REGEN-COV), other litigation and other proceedings and government investigations relating to the Company and/or its operations, the ultimate outcome of any such proceedings and investigations, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the U.S. Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2020. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update (publicly or otherwise) any forward-looking statement, including any financial projection or guidance, whether as a result of new information, future events, or otherwise.*

*Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (http://newsroom.regeneron.com) and its Twitter feed (http://twitter.com/regeneron).*

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