



Regeneron Announces Encouraging Initial Data from COVID-19 Antibody Cocktail Trial in Hospitalized Patients on Low-flow Oxygen

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Phase 3 program in hospitalized patients to continue based on passing futility analysis on ability to reduce incidence of death or mechanical ventilation

As in earlier outpatient trial, immune status when patients entered the trial was a strong predictor of viral load and clinical outcomes

First antibody therapy to demonstrate anti-viral effect in patients hospitalized with COVID-19

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced encouraging initial data from an ongoing Phase 1/2/3 clinical trial of the Regeneron antibody cocktail, casirivimab and imdevimab, in hospitalized COVID-19 patients requiring low-flow oxygen. The analysis was prospectively designed to focus on patients who had not yet mounted their own immune response to SARS-CoV-2 (i.e., did not have antibodies at baseline: seronegative), as prior evidence suggested these patients were at greater risk. The primary clinical objective of this initial analysis was to determine if there was sufficient efficacy in these patients to warrant continuing the trial (i.e., futility analysis). The results passed the futility analysis ($p < 0.3$ one-sided), as seronegative patients treated with the antibody cocktail had a lower risk of death or receiving mechanical ventilation (HR: 0.78; 80% CI: 0.51-1.2). The benefit was driven by results starting one week post-treatment, when the risk of death or receiving mechanical ventilation was reduced by approximately half with antibody cocktail treatment, based on a post-hoc analysis.

Seronegative patients ($n=217$) had much higher viral loads than those who had already developed their own antibodies (seropositive) to SARS-CoV-2 at the time of randomization. In seronegative patients, the antibody cocktail reduced the time-weighted average daily viral load through day 7 by $-0.54 \log_{10}$ copies/mL, and through day 11 by $-0.63 \log_{10}$ copies/mL (nominal $p=0.002$ for combined doses). At day 5, the relative reduction compared to placebo was $-1.1 \log_{10}$ copies/mL (nominal $p=0.002$ for combined doses). As expected, in seropositive patients ($n=270$) the clinical and virologic benefit of the antibody cocktail was limited (clinical endpoint HR: 0.98; time-weighted average viral load reduction by day 7 of $-0.20 \log_{10}$ copies/mL for combined doses).

"These preliminary results in hospitalized patients, as well as data from the previously announced outpatient trial, indicate that antibodies produced by a patient's own immune response are important to control COVID-19 infection. In this trial, patients who had not yet mounted their own immune response had much higher viral loads and much worse clinical outcomes; for example in the placebo group, seronegative patients were almost three-times more likely to die compared to seropositive patients," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "Moreover, the data from these trials in hospitalized and non-hospitalized patients suggest that Regeneron's antibody cocktail may compensate for an inadequate endogenous antibody response by reducing viral levels and the risk of adverse clinical outcomes. It is important to remember that while the virology results from this analysis of hospitalized patients were robust, the clinical efficacy data are based on a small data set of events and cannot be viewed as conclusive at this stage. A much larger trial will be required to rigorously characterize this effect and we believe the ongoing UK-based [RECOVERY](#) trial will provide those answers. It has already enrolled more than 2,000 hospitalized patients in the part of the trial evaluating adding the antibody cocktail to standard-of-care compared to standard-of-care alone."

The clinical and virological analyses include data from the Regeneron-sponsored trial evaluating hospitalized patients who were on low-flow oxygen (defined as maintaining oxygen saturation of $>93\%$ via nasal cannula, simple facemask, or similar device), including 217 who were seronegative when they entered the trial and 270 who were seropositive; although seronegative patients comprised less than half of the trial population, based on placebo rates they account for approximately two-thirds of the deaths in the absence of antibody cocktail treatment. Patients were randomized to receive the antibody cocktail (either 8,000 mg high dose or 2,400 mg low dose) or placebo, in addition to standard-of-care therapies, with 67% receiving remdesivir and 74% receiving systemic corticosteroids. Similar clinical and virologic efficacy was observed for the high and low doses of the antibody cocktail.

Both antibody cocktail doses were well-tolerated. In the overall trial population, the incidence of serious adverse events was 21% for high dose, 20% for low dose and 24% for placebo. Infusion reactions were more common with the high dose of the antibody cocktail (2.7% high dose, 0.9% low dose, 1.4% placebo) and there were 2 discontinuations due to infusion-related reactions, both of which occurred in the high dose group.

In [November](#), the Regeneron antibody cocktail was granted an Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA) in high-risk patients who have confirmed COVID-19 but are not currently hospitalized. The EUA is temporary and does not take the place of a formal biologics license application (BLA) submission review and approval process and the use of the antibody cocktail remains investigational. Evaluation of its safety and efficacy is ongoing in multiple clinical trials.

"We appreciate the continued support of patients and investigators around the world who are working to advance Regeneron's antibody cocktail trials under very challenging circumstances," said David Weinreich, M.D., Senior Vice President and Head of Global Clinical Development at Regeneron. "Hospitalizations due to COVID-19 are increasing around the globe and have devastating consequences for these patients, their families and those who care for them, highlighting the need for effective therapeutics. We plan to share these most recent data with regulatory authorities."

Regeneron announced in [October](#) that the hospitalized trial would be modified to no longer enroll the most critical patients requiring high-flow oxygen or mechanical ventilation at baseline, following a recommendation by the Independent Data Monitoring Committee. The UK RECOVERY trial continues to recruit all hospitalized patients regardless of the degree of severity, based on a recommendation from its Independent Data Monitoring

Committee.

In addition to the two hospitalized patient trials (company-sponsored and UK-based RECOVERY trial), the antibody cocktail is currently being studied in a Phase 3 trial for the treatment of non-hospitalized patients, and a Phase 3 trial for the prevention of COVID-19 in household contacts of infected individuals.

Under an agreement with the U.S. government, Regeneron is producing approximately 300,000 doses (2,400 mg) for outpatient use under the EUA. The company expects to complete the manufacture of these doses on schedule in January 2021 and is in discussions with the U.S. government regarding additional doses.

In the U.S., outside of clinical trials casirivimab and imdevimab are not authorized for use in patients who are hospitalized or require oxygen therapy due to COVID-19, 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.

About the Regeneron Trial in Hospitalized Patients

The analysis includes patients enrolled in the Phase 1/2 portions of the trial, which was designed to evaluate clinical outcomes, safety and anti-viral activity with the casirivimab and imdevimab antibody cocktail for COVID-19. Patients were randomized 1:1:1 to receive a one-time infusion of 8,000 mg of the antibody cocktail (high dose), 2,400 mg of the antibody cocktail (low dose) or placebo. All patients entering the trial were hospitalized with laboratory-confirmed COVID-19 requiring low-flow oxygen, and all received other background standard-of-care as required.

All patients were characterized for their serology at baseline: approximately 50% of patients were seropositive, 40% were seronegative and 10% were categorized as "other" due to unclear or unknown serology status. Approximately 24% were Hispanic and 14% were African American. On average, patients were 62 years of age. In total, 53% of participants were male and 47% were female.

About Regeneron Antibody Cocktail

Casirivimab and imdevimab is a cocktail of two monoclonal antibodies (also known as REGN10933 and REGN10987, respectively) and was designed specifically to block infectivity of SARS-CoV-2, the virus that causes COVID-19.

On [November 21, 2020](#), the casirivimab and imdevimab antibody combination received EUA from the FDA for the treatment of 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. The clinical evidence from Regeneron's outpatient trial suggests that monoclonal antibodies such as casirivimab and imdevimab have the greatest benefit when given early after diagnosis and in patients who are seronegative and/or who have high viral load. The criteria for 'high-risk' patients are described in the [Fact Sheet for Healthcare Providers](#).

To develop this novel medicine, Regeneron scientists evaluated thousands of fully-human antibodies produced by the company's *VelocImmune*[®] mice, which have been genetically modified to have a human immune system, as well as antibodies identified from humans who have recovered from COVID-19. 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](#).

The development and manufacturing of the antibody cocktail has 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 (HHS), Office of the Assistant Secretary for Preparedness and Response, under OT number: HHSO100201700020C. Regeneron continues to increase in-house production of casirivimab and imdevimab, and the company has [partnered](#) with Roche to increase the global supply beginning in 2021. If the therapy proves safe and effective in clinical trials and regulatory approvals are granted, Regeneron will manufacture and distribute it in the U.S. and Roche will develop, manufacture and distribute it outside the U.S. Once both companies are at full manufacturing capacity in 2021, there are expected to be at least 2 million treatment doses available annually.

AUTHORIZED USE AND IMPORTANT SAFETY INFORMATION

Authorized Emergency Use

Casirivimab and imdevimab injection is an investigational combination therapy and has been authorized by FDA for the emergency use described above. Casirivimab and imdevimab injection is not FDA approved for any use. Safety and effectiveness of casirivimab and imdevimab injection have not yet been established for the treatment of COVID-19.

This authorized use is 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.

Limitations of Authorized Use

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

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 ≥ 85 th percentile for their age and gender based on CDC growth charts, 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.

Warnings and Precautions:

- **Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions:** There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of casirivimab and imdevimab injection. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Infusion-related reactions have been observed with administration of casirivimab and imdevimab injection. Signs and symptoms of infusion related reactions may include fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and/or dizziness. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.
- **Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19:** Benefit of treatment with casirivimab and imdevimab injection has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients requiring high flow oxygen or mechanical ventilation with COVID-19. Therefore, casirivimab and imdevimab injection is not authorized for use in 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 the casirivimab and imdevimab injection 2,400 mg group, 2 (0.8%) patients in casirivimab and imdevimab injection 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 casirivimab and imdevimab injection), intestinal obstruction and dyspnea (8,000 mg casirivimab and imdevimab injection) and COVID-19, pneumonia and hypoxia (placebo). Casirivimab and imdevimab injection are not authorized at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).

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 casirivimab and imdevimab injection in COVID-19 patients who are pregnant. Casirivimab and imdevimab injection therapy should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.
- **Nursing Mothers:** There is currently no clinical experience in use of casirivimab and imdevimab injection 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 casirivimab and imdevimab injection and any potential adverse effects on the breastfed child from casirivimab and imdevimab injection 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 eight FDA-approved treatments and numerous product candidates in development, 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, 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.

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 (including those discussed in this press release), 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 without limitation the development program relating to casirivimab and imdevimab (Regeneron's investigational multi-antibody therapy for the treatment and prevention of COVID-19); how long the Emergency Use Authorization ("EUA") granted by the U.S. Food and Drug Administration (the "FDA") for casirivimab and imdevimab 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 (such as casirivimab and imdevimab) and new indications for Regeneron's Products; safety issues resulting from the administration of Regeneron's Products and product candidates (such as casirivimab and imdevimab) in patients, including serious complications or side effects in connection with the use of Regeneron's Products and product candidates in clinical trials (including those discussed in this press release); the ability of Regeneron to manufacture in anticipated quantities Regeneron's Products and product candidates, including casirivimab and imdevimab; the ability of Regeneron to manage supply chains for multiple products and product candidates; 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; uncertainty of market acceptance and commercial success of Regeneron's Products and product candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary), including the trials discussed in this press release, on any potential regulatory approval (including with respect to casirivimab and imdevimab) and/or the commercial success of Regeneron's Products and product candidates; 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 without limitation casirivimab and imdevimab; 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 casirivimab and imdevimab, to be cancelled or terminated; and risks associated with intellectual property of other parties and pending or future litigation relating thereto (including without limitation the patent litigation and other related proceedings relating to EYLEA[®] (afibercept) Injection, Dupixent[®] (dupilumab), and Praluent[®] (alirocumab)), 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, 2019 and its Form 10-Q for the quarterly period ended September 30, 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 without limitation 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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[trial-in-hospitalized-patients-on-low-flow-oxygen-301199163.html](https://www.fda.gov/oc/ohrt/trial-in-hospitalized-patients-on-low-flow-oxygen-301199163.html)

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