EMA issues advice on Lilly's bamlanivimab (LY-CoV555) alone and administered together with etesevimab (LY-CoV016) for the treatment of confirmed COVID-19 in the European Union

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CHMP has completed a review of available data for both antibodies for the treatment of confirmed COVID-19
CHMP scientific opinion supports national decision-making within European Union (EU) member states on the use of the antibodies during a public health emergency before a formal marketing authorization is granted

INDIANAPOLIS, March 5, 2021 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has issued a positive scientific opinion for bamlanivimab alone and bamlanivimab administered together with etesevimab. The opinion advises bamlanivimab alone and bamlanivimab administered together with etesevimab can be used for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19. The CHMP scientific opinion under Article 5.3 of regulation 726/2004 provides a harmonized, EU-level opinion on the efficacy, quality, and safety of the antibodies. The opinion can now be considered by the EU member states when making decisions on the use of the therapies at a national level before a formal marketing authorization is issued.

"Today's CHMP recommendation is another important milestone in our efforts to extend access to antibody therapies for patients with COVID-19 around the world, providing a pathway for more EU countries to enable use of potentially life-saving treatments for COVID-19. In addition, other countries look to CHMP advice to support their own reviews. We hope this opinion will accelerate those reviews and authorizations, particularly in low- and middle-income countries, where Lilly is prepared to provide doses at greatly reduced costs or free of charge," said David A. Ricks, Lilly's chairman and CEO. "Lilly is proud that hundreds of thousands of patients globally have already received treatment with our antibody therapy, and we will continue to deliver on our commitment to help high-risk patients who may benefit as the world works to fight this pandemic."

To support the opinion, the EMA reviewed Phase 2 and Phase 3 results from Lilly's BLAZE-1 trial. Results from BLAZE-1 demonstrated bamlanivimab alone reduced viral load and symptoms and also reduced COVID-19 hospitalizations by approximately 70 percent, and bamlanivimab and etesevimab together reduced the risk of COVID-19 hospitalizations and death by 70 percent in non-hospitalized high-risk patients with mild to moderate COVID-19.

Lilly Antibody Therapies Around the World
Lilly continues to engage with global regulators regarding the potential of both bamlanivimab alone and bamlanivimab and etesevimab together in treating COVID-19, working with regulators to make these therapies available around the world. The company is focused on areas with the highest disease burden and global allocations are made based on Lilly's guiding principles that aim to ensure access for patients with high unmet need, no matter where they live. Bamlanivimab alone is authorized under special/emergency pathways, in the context of the pandemic, in numerous countries – including Canada, the Czech Republic, Germany, Israel, Italy, Hungary, Sweden, UAE and the U.S. – while bamlanivimab and etesevimab together is currently authorized for emergency use in the U.S. and Italy. In addition, bamlanivimab alone has been authorized for emergency use in Rwanda and Morocco, and through Lilly's work with the Bill & Melinda Gates Foundation, Lilly is providing doses of the medicine free of charge in these countries.

For media resources, including product images and fact sheets, please click here.

Important Information about bamlanivimab alone and bamlanivimab and etesevimab together
Bamlanivimab and etesevimab together and bamlanivimab alone have not been approved by the FDA for any use. It is not known if bamlanivimab and etesevimab together or bamlanivimab alone are safe and effective for the treatment of COVID-19.

Bamlanivimab and etesevimab together and bamlanivimab alone are authorized under Emergency Use Authorization 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 information on the authorized use of bamlanivimab and etesevimab together and bamlanivimab alone and mandatory requirements of the EUA. Please see the FDA Letter of Authorization, Fact Sheet for Healthcare Providers, and Fact Sheet for Patients, Parents and Caregivers (English) (Spanish) for bamlanivimab and etesevimab together. Please see the FDA Letter of Authorization, Fact Sheet for Healthcare Providers, and Fact Sheet for Patients, Parents and Caregivers (English) (Spanish) for bamlanivimab alone.

U.S. Authorized Use and Important Safety Information
Bamlanivimab 700 mg and etesevimab 1400 mg together and bamlanivimab 700 mg alone are authorized for use under EUA for 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

- Bamlanivimab and etesevimab together and bamlanivimab alone are not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

- Treatment with bamlanivimab and etesevimab together has not been studied in patients hospitalized due to COVID-19. Benefit of treatment with bamlanivimab alone has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Important Safety Information
There are limited clinical data available for bamlanivimab and etesevimab together and bamlanivimab alone. Serious and unexpected adverse events may occur that have not been previously reported with bamlanivimab and etesevimab together and bamlanivimab alone.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions
Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab and etesevimab together and bamlanivimab alone. If signs and 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 bamlanivimab and etesevimab together and bamlanivimab alone. 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, arrhythmia (e.g. atrial fibrillation, sinus 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 Bamlanivimab Administration
Clinical worsening of COVID-19 after administration of bamlanivimab has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.

Limitations of Benefit and Potential Risk in Patients with Severe COVID-19
Treatment with bamlanivimab and etesevimab together has not been studied in patients hospitalized due to COVID-19. Benefit of treatment with bamlanivimab alone has not been observed in patient hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. See Limitations of Authorized Use.

Adverse Events
Bamlanivimab and etesevimab together
Based on Phase 2 data from BLAZE-1, nausea was the most commonly reported adverse event, reported by 4% of subjects in both bamlanivimab and etesevimab together and placebo groups. Pruritus and pyrexia were more frequently reported from subjects treated with both bamlanivimab and etesevimab (2% and 1%) compared to placebo (1% and 0%, respectively).

Based on Phase 3 data from BLAZE-1, the most common adverse events were nausea, dizziness, and rash. These events each occurred in 1% of subjects treated with bamlanivimab and etesevimab together and in 1% of placebo subjects.

Bamlanivimab alone
Adverse events reported in at least 1% of BLAZE-1 clinical trial participants on bamlanivimab 700 mg alone or placebo were nausea (3% vs 4%), diarrhea (1% vs 5%), dizziness (3% vs 2%), headache (3% vs 2%), pruritus (2% vs 1%) and vomiting (1% vs 3%).

Use in Specific Populations
Pregnancy
There are insufficient data on the use of bamlanivimab and etesevimab together and bamlanivimab alone during pregnancy. Bamlanivimab and etesevimab together and bamlanivimab alone should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Breastfeeding
There are no available data on the presence of bamlanivimab or etesevimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

About bamlanivimab
Bamlanivimab is a recombinant, neutralizing human IgG1 monoclonal antibody (mAb) directed against the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus, potentially treating COVID-19. Bamlanivimab emerged from the collaboration between Lilly and AbCellera to create antibody therapies for the prevention and treatment of COVID-19. Lilly scientists rapidly developed the antibody in less than three months after it was discovered by AbCellera and the scientists at the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center. It was identified from a blood sample taken from one of the first U.S. patients who recovered from COVID-19.

Lilly has successfully completed a Phase 1 study of bamlanivimab in hospitalized patients with COVID-19 (NCT04411628). A Phase 2/3 study in people recently diagnosed with COVID-19 in the ambulatory setting (BLAZE-1, NCT04427501) is ongoing. A Phase 3 study of bamlanivimab for the prevention of COVID-19 in residents and staff at long-term care facilities (BLAZE-2, NCT04497987) is also ongoing. In addition, bamlanivimab is being tested in the National Institutes of Health-led ACTIV-2 study in ambulatory COVID-19 patients.

About etesevimab
Etesevimab (LY-CoV016, also known as JS016) is a recombinant fully human monoclonal neutralizing antibody, which specifically binds to the

SARS-CoV-2 surface spike protein receptor binding domain with high affinity and can block the binding of the virus to the ACE2 host cell surface receptor. Point mutations were introduced into the native human IgG1 antibody to mitigate effector function. Lilly licensed etesevimab from Junshi Biosciences after it was jointly developed by Junshi Biosciences and the Institute of Microbiology, Chinese Academy of Science (IMCAS). Junshi Biosciences leads development in Greater China, while Lilly leads development in the rest of the world.

Lilly has successfully completed a Phase 1 study (NCT04441931) of etesevimab in healthy U.S. volunteers to evaluate the safety, tolerability, pharmacokinetics and immunogenicity. A Phase 2/3 study in people recently diagnosed with COVID-19 in the ambulatory setting (BLAZE-1, NCT04427501) is ongoing. Junshi Biosciences has completed a similar Phase 1 study in healthy volunteers in China and has initiated Phase 1b/2 trials in COVID-19 patients globally.

About BLAZE-1
BLAZE-1 (NCT04427501) is a randomized, double-blind, placebo-controlled Phase 2/3 study designed to assess the efficacy and safety of bamlanivimab alone or bamlanivimab and etesevimab together for the treatment of symptomatic COVID-19 in the outpatient setting. To be eligible, patients were required to have mild or moderate symptoms of COVID-19 as well as a positive SARS-CoV-2 test based on a sample collected no more than three days prior to drug infusion.

In the Phase 2 portion of BLAZE-1, cohorts of mild to moderate recently diagnosed COVID-19 patients, were randomized to one of three doses of bamlanivimab (700 mg, 2800 mg, and 7000 mg), bamlanivimab 2800 mg plus etesevimab 2800 mg, or placebo. Results from the Phase 2 cohorts of BLAZE-1 were published in the *New England Journal of Medicine* and *The Journal of the American Medical Association*.

In the Phase 3 portion of BLAZE-1, the combination therapy arms enrolled mild to moderate, recently diagnosed COVID-19 patients who are at high risk for progressing to severe COVID-19 and/or hospitalization, studying bamlanivimab 2800 mg plus etesevimab 2800 mg versus placebo. The primary outcome measure for the Phase 3 portion of the BLAZE-1 trial was the percentage of participants who experience COVID-related hospitalizations or death from any cause by day 29. The key secondary endpoints were change from baseline to day 7 in SARS-CoV-2 viral load, persistently high SARS-CoV-2 viral load on day 7, time to sustained symptom resolution, and COVID-related hospitalization, ER visit or death from any cause from baseline by day 29. Additional endpoints include change from baseline in viral load at other time points, symptom improvement, symptom resolution, as well as safety.

The study is ongoing with additional treatment arms. Across all treatment arms, the trial will enroll up to 3,300 participants.

About Lilly's COVID-19 Efforts
Lilly is bringing the full force of its scientific and medical expertise to attack the coronavirus pandemic around the world. Existing Lilly medicines are being studied to understand their potential in treating complications of COVID-19, and the company is collaborating with partner companies to discover and develop novel antibody treatments for COVID-19. Lilly is testing both single antibody therapy as well as combinations of antibodies as potential therapeutics for COVID-19. Click here for resources related to Lilly's COVID-19 efforts.

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to create medicines that make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com and www.lilly.com/news. P-LLY

Lilly Cautionary Statement Regarding Forward-Looking Statements
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about bamlanivimab (LY-CoV555) alone or bamlanivimab and etesevimab (LY-CoV016) together as potential treatments for patients with COVID-19, as well as its supply and distribution, and reflects Lilly's current beliefs and expectations. However, as with any such undertaking, there are substantial risks and uncertainties in the process of drug development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date, that bamlanivimab alone or bamlanivimab and etesevimab together will prove to be safe and effective treatments or successful preventative therapies for COVID-19, that bamlanivimab alone or bamlanivimab and etesevimab together will receive regulatory approvals or additional authorizations, or that Lilly can provide an adequate supply of bamlanivimab alone or bamlanivimab and etesevimab together in all circumstances. For a further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see Lilly's most recent Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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