Lilly's bamlanivimab (LY-CoV555) administered with etesevimab (LY-CoV016) receives FDA emergency use authorization for COVID-19

February 10, 2021

- Bamlanivimab and etesevimab administered together authorized for treatment of recently diagnosed, mild to moderate COVID-19 in patients who are high risk for progression to severe COVID-19

- More than 250,000 doses manufactured throughout Q1 2021; up to 1 million doses by mid-2021

- FDA authorizes shortened infusion time for both of Lilly's neutralizing antibody therapies authorized for emergency use

INDIANAPOLIS, Feb. 9, 2021 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for investigational bamlanivimab (LY-CoV555) 700 mg and etesevimab (LY-CoV016) 1400 mg together, Eli Lilly and Company (NYSE: LLY) announced today. This therapy is authorized for the treatment of mild to moderate COVID-19 in patients aged 12 and older who are at high risk for progressing to severe COVID-19 and/or hospitalization. Bamlanivimab and etesevimab should be administered together via a single intravenous infusion as soon as possible after a positive COVID-19 test and within 10 days of symptom onset.

In addition, the FDA has authorized infusion times for bamlanivimab alone and bamlanivimab and etesevimab together to be as short as 16 or 21 minutes, respectively – a significant reduction from the previously authorized time of 60 minutes. This decision has been made in response to feedback received from front-line nurses and doctors administering these infusions and are aimed at reducing the burden on the healthcare system.

"Lilly has dedicated our time, resources, and expertise to discover and develop therapies to treat COVID-19," said Daniel Skovronsky, M.D., Ph.D., Lilly's chief scientific officer and president of Lilly Research Laboratories. "Bamlanivimab alone under emergency use authorization has already provided many people with an early treatment option that could prevent hospitalizations and we are excited to now add an additional therapeutic option with a similar demonstrated clinical benefit. Additionally, with the risk of resistance emerging as various strains of the virus arise, bamlanivimab and etesevimab together could potentially allow efficacy against a broader range of naturally occurring SARS-CoV-2 variants as these new strains spread around the world."

The EUA is based on Phase 3 data from the BLAZE-1 trial, announced January 26, 2021, which demonstrated bamlanivimab and etesevimab together reduced the risk of COVID-19 hospitalizations and death by 70 percent. These data replicate earlier results, published in *The Journal of the American Medical Association*, in a much larger group of patients. Additionally, the outcomes seen with bamlanivimab and etesevimab together are consistent with the reduction in risk of hospitalization or ER visits seen with bamlanivimab alone. The most common adverse event more often reported for patients receiving bamlanivimab and etesevimab together versus placebo was nausea on the day of infusion.

While Phase 2 and Phase 3 trials evaluated a range of doses of bamlanivimab alone and bamlanivimab and etesevimab together, data demonstrated consistent and similar clinical effects among all doses studied. Additionally, initial results from an ongoing Phase 2 study provide viral load and pharmacodynamic/pharmacokinetic data which demonstrated bamlanivimab 700 mg and etesevimab 1400 mg together produced similar effects to those observed in the Phase 3 trial with bamlanivimab 2800 mg and etesevimab 2800 mg together. Together, these data provide confidence in the authorized dose, which expands available supply to help more patients without sacrificing potential efficacy.

The FDA grants EUA to provide availability of a medicine that may help diagnose, treat or prevent a life-threatening disease when no adequate and approved alternatives are available. This administration of bamlanivimab and etesevimab together is authorized only for the duration of the declaration, unless the authorization is terminated or revoked sooner. The authorization is temporary and does not replace the formal review and approval process. The administration of bamlanivimab and etesevimab together remains investigational and has not been approved under a Biologics License Application (BLA). Evaluation of its safety and efficacy is ongoing in clinical trials. Data from these studies will be used to support a future BLA submission for the treatment.

Bamlanivimab alone is authorized in numerous countries, while bamlanivimab and etesevimab together is currently authorized in the U.S. and Italy. Lilly will continue working with global regulators to make these therapies available around the world. In an effort to help as many patients as possible, Lilly will continue to supply bamlanivimab alone under the authorizations granted in various countries while continuing to accelerate manufacturing of etesevimab for use around the world. Lilly, in collaboration with Amgen, plans to manufacture up to 1 million doses of etesevimab for administration with bamlanivimab by mid-2021. There are 100,000 doses ready immediately and an additional 150,000 doses will be available throughout the first quarter.

"As COVID-19 cases, hospitalizations and subsequent deaths continue to rise, we are committed to working with the U.S. government to supply our antibody therapies for use by patients across the country," Skovronsky added.

Lilly anticipates procurement and allocation of bamlanivimab and etesevimab together will mirror the process followed for bamlanivimab alone – making the therapy available directly to governments for allocation based on unmet needs. Global allocation will be made based on Lilly's guiding principles that aim to ensure access for patients with high unmet need, no matter where they live.

For more information about the use of bamlanivimab alone or bamlanivimab and etesevimab together for the treatment of mild to moderate COVID-19 in high-risk patients under the FDA's emergency use authorization, contact Lilly's 24-hour support line at 1-855-LillyC19 (1-855-545-5921). Patients and physicians can visit covid.infusioncenter.org or the HHS Therapeutics Distribution locator to find a potential treatment location.

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.

Authorized Use and Important Safety Information
Bamlanivimab and etesevimab together and bamlanivimab 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 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 BLAZE-4
BLAZE-4 (NCT04634409) is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of bamlanivimab alone, and bamlanivimab and etesevimab together, at various doses, versus placebo for the treatment of symptomatic COVID-19 in the outpatient setting. Across all treatment arms, the trial will enroll an estimated 1,000 participants in the United States and Puerto Rico.

The primary outcome measure is percentage of participants who have a viral load greater than 5.27 at day 7. Additional endpoints include change from baseline to day 7 in SARS-CoV-2 viral load, percentage of participants who experience COVID-related hospitalization, ER visit or death from baseline through day 29, as well as safety.

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 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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