

**Emergency Use Authorization (EUA) for  
Bamlanivimab 700 mg and Etesevimab 1,400 mg  
Center for Drug Evaluation and Research (CDER) Review**

**Identifying Information**

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	EUA 000094
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Eli Lilly and Company Christine Phillips, PhD, RAC Advisor, Global Regulatory Affairs - NA Mobile: (b) (6) Email: phillips_christine_ann@lilly.com
Manufacturer, if different from Sponsor	Eli Lilly and Company
Submission Date(s)	February 16, 2021
Receipt Date(s)	February 16, 2021
OND Division / Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)/Discipline(s)	Natalie Pica, MD, PhD – Clinical Reviewer Wendy Carter, DO – Cross Discipline Team Lead Michael Thomson, PhD – Clinical Virology Reviewer Jules O'Rear, PhD – Clinical Virology Team Lead Daniel Rubin, PhD – Statistics Reviewer Thamban Valappil, PhD – Statistics Team Lead Dionne Price, PhD – Director, Division of Biometrics IV Jason Moore, PharmD – Clinical Pharmacology Reviewer Su-Young Choi, PharmD, PhD – Clinical Pharmacology Team Lead Kellie Reynolds, PharmD – Division Director, DIDP Ye Xiong, PhD – Pharmacometrics Reviewer Justin Earp, PhD – Pharmacometrics Team Lead Deacqunita Diggs, PhD – Pharmacology/Toxicology Reviewer Christopher Ellis, PhD – Pharmacology/Toxicology Team Lead

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Integrated Review Completion Date	September 15, 2021
Proprietary Name	n/a
Established Name/Other names used during development	Bamlanivimab (BAM, LY3819253; LY-CoV555) and Etesevimab (ETE, LY3832479; LY-CoV016)
Dosage Forms/Strengths	Bamlanivimab - 700mg IV Etesevimab – 1,400mg IV
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1k monoclonal antibodies (mAbs)
Intended Use or Need for EUA	<p>Treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adult 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 progression to severe COVID-19, including hospitalization or death.</p> <p>Post-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:</p> <ul style="list-style-type: none"> <li>• not fully vaccinated <b>or</b> who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications) <b>and</b> <ul style="list-style-type: none"> <li>○ have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria</li> </ul> </li> </ul>

	<p>per Centers for Disease Control and Prevention (CDC) <b>or</b></p> <ul style="list-style-type: none"> <li>o who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).</li> </ul>
Intended Population(s)	Adults and pediatric patients (12 years of age and older weighing at least 40 kg)
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	Please refer to the Letter of Authorization for details.

## I. **EUA Determination/Declaration**

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus was named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

## II. **Recommendations**

### A. **Recommend EUA Issuance**

Bamlanivimab and etesevimab are 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 progression to severe COVID-19, including hospitalization and death.

Following review of data submitted by the Applicant, The Division of Antivirals, Office of Infectious Diseases, Office of New Drugs, CDER recommends issuance of a revision to EUA 94, allowing for the additional use of bamlanivimab and etesevimab administered together for the purposes of post-exposure prophylaxis for prevention of SARS-CoV-2 infection for the following use:

- Post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
  - not fully vaccinated<sup>1</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>3</sup> **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons)

## B. Summary of Regulatory Actions for EUA 94

On [February 9, 2021](#) bamlanivimab and etesevimab were authorized under EUA 94 for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kilograms (about 88 pounds), and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

On [February 25, 2021](#) the Letter of Authorization was reissued to revise the process for the development and dissemination of instructional and educational materials and facilitate the Agency's evaluation of any emerging global viral variants, including the assessment and potential impact on the authorized bamlanivimab and etesevimab.

On [March 17, 2021](#) the Fact Sheet for Health Care Providers was updated to include antiviral resistance information for bamlanivimab and etesevimab administered together.

On [May 7, 2021](#), FDA and the Office of the Assistant Secretary for Preparedness and Response (ASPR) paused distribution of bamlanivimab and etesevimab

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<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>

together and etesevimab alone (to pair with existing supply of bamlanivimab) to the state of Illinois due to the P.1 variant, that was circulating with increasing frequency within the state of Illinois.

On [May 14, 2021](#) the Fact Sheet for Health Care Providers and the Fact Sheet for Patients, Parents and Caregivers were updated to expand the definition of high risk to include additional medical conditions and other factors, remove the rationale for the authorized dose because Phase 3 data confirmed the authorized dose, updated safety analyses, added information on the susceptibility of SARS-CoV-2 variants to bamlanivimab and etesevimab and added Phase 3 clinical trial results.

From [May 21, 2021](#) through June 15, 2021, FDA and ASPR paused distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing supply of bamlanivimab) to additional states, as the frequency of SARS-CoV-2 variants expected to be resistant to bamlanivimab and etesevimab increased in these states. Ultimately, on [June 25, 2021](#), all distribution of bamlanivimab and etesevimab together and etesevimab alone was nationally paused due to the combined frequency of P.1(Gamma) and B.1.351(Beta) variants exceeding 11% throughout the U.S.

On [August 20, 2021](#) FDA and ASPR announced a shelf life extension of bamlanivimab under the EUA for bamlanivimab and etesevimab administered together, extending the shelf life from 12 months to 18 months.

On [August 27, 2021](#), FDA and ASPR announced the resumption in use and distribution of bamlanivimab and etesevimab in 22 states in the HHS regions 1, 5, 7 and 8 based on data showing the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5% in these states. A [Limitations of Authorized Use for bamlanivimab and etesevimab](#), administered together, was added to the Fact Sheet for Health Care Providers to only authorize use in states, territories, and U.S. jurisdictions where the combined frequency of variants resistant to bamlanivimab and etesevimab, administered together, is less than or equal to 5%.

On [September 2, 2021](#), FDA and ASPR announced resumption in use and distribution of bamlanivimab and etesevimab in all U.S. states, territories and jurisdictions under the [updated conditions of authorization for EUA 94](#). The updated letter of authorization clarified the meaning of “severe COVID-19” and further limited the use of bamlanivimab and etesevimab authorizing bamlanivimab and etesevimab administered together only in those states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%. Revisions were also incorporated to the conditions on compliance with cGMPs, product quality reporting, requests for CMC (chemistry, manufacturing and controls) changes to this authorization, the provision of samples of the authorized bamlanivimab and

etesevimab to HHS, upon request, and the conditions on advertising and promotion.

### C. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.
- Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2.
- Based on the totality of the scientific evidence available to FDA, including a topline analysis of data from BLAZE-2 Part 1 (also known as Trial J2X-MC-PYAD; NCT04497987), a Phase 3 randomized, double-blind, placebo-controlled trial evaluating bamlanivimab alone for prevention of COVID-19 in residents and staff of skilled nursing facilities following a confirmed reported case of SARS-CoV-2 infection at the facility, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for post-exposure prophylaxis of COVID-19 in certain individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, **and** are not fully vaccinated<sup>2</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>4</sup>), **and** have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC<sup>3</sup> **or** who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons); and under such conditions, the known and potential benefits outweigh the known and potential risks of the drugs.
  - There is no adequate, approved, and available alternative to the emergency use of bamlanivimab and etesevimab administered for use as post-exposure prophylaxis of COVID-19, as described above.
  - At present, there are three COVID-19 vaccines authorized for emergency use to prevent COVID-19. The Pfizer-BioNTech and Moderna vaccines are vaccines that include nucleoside-modified messenger RNA that encodes the viral spike glycoprotein of SARS-CoV-2 and are administered as a 2-dose series. The Janssen/Johnson & Johnson vaccine is a replication-incompetent recombinant adenovirus type 26 vector expressing the SARS-CoV-2 spike protein in a stabilized conformation and is administered intramuscularly as a single dose. The Pfizer-BioNTech vaccine is approved for individuals age 16 and older; it is authorized for emergency use in individuals 12 -15 years of age. The Moderna and Janssen/Johnson & Johnson vaccines are authorized for individuals 18 years of age and older.

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<sup>4</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>

### III. Proposed Use and Dosing of the Product Under the EUA

#### Proposed Use Under EUA:

We recommend that EUA 94 now authorize bamlanivimab and etesevimab administered together for emergency use as post-exposure prophylaxis for COVID-19, in addition to the already authorized use of treatment of mild to moderate COVID-19, as detailed below. The Limitations of Authorized Use related to resistant variants will apply to both the treatment and post-exposure prophylaxis uses; additional Limitations of Authorized Use for post-exposure prophylaxis related to COVID-19 vaccination and pre-exposure prophylaxis should be added.

#### *Treatment*

The EUA authorizes the emergency use of unapproved products bamlanivimab and etesevimab administered together in adults and pediatric patients (12 years of age and older weighing at least 40 kg) for the treatment of patients with documented SARS-CoV-2 infection who are at high risk for progression to severe COVID-19, including hospitalization or death.

Limitations of Authorized Use for Treatment:

#### Combined Frequency of Variants Resistant to Bamlanivimab and Etesevimab

- Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.<sup>5</sup>
  - A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website:  
<https://www.fda.gov/media/151719/download>

#### Use in Patients Who Are Hospitalized or Who Require Oxygen Due to COVID-19

- Bamlanivimab and etesevimab 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.

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<sup>5</sup> FDA will make this determination considering current variant frequency data (available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

- Treatment with bamlanivimab and etesevimab has not been studied 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.

### *Post-Exposure Prophylaxis*

We recommend that the EUA now permit the use of bamlanivimab and etesevimab administered together for post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated<sup>6</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>7</sup>) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>8</sup> **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

### Limitations of Authorized Use for Post-Exposure Prophylaxis:

- Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.<sup>9</sup>

<sup>6</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>

<sup>7</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>

<sup>8</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>

<sup>9</sup> FDA will make this determination considering current variant frequency data (available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.



- A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website:  
<https://www.fda.gov/media/151719/download>
- Post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19.
- Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

### Authorized Dosage Under EUA:

#### *Adults and Pediatric Patients:*

The authorized treatment dosage is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as a single intravenous (IV) infusion as soon as possible after positive viral test for SARS-CoV-2 and within ten days of symptom onset.

With revision of the EUA, the authorized post-exposure prophylaxis dosage is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as a single IV infusion as soon as possible after exposure to an individual infected with SARS-CoV-2, and the exposure meets close contact criteria per CDC.

#### *Pregnant or Lactating Patients:*

No dosage adjustment is recommended for pregnant or lactating patients. Bamlanivimab and etesevimab are currently being studied in pregnant women but have not yet been studied in lactating women. Bamlanivimab and etesevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

#### *Other Specific Populations (e.g., Geriatric Patients, Patients with Renal or Hepatic Impairment):*

No dose adjustment is recommended based on age (12 to 86 years of age), sex, race, body weight (41 kg to 173 kg), renal impairment, and mild hepatic impairment. Bamlanivimab and etesevimab have not been studied in patients with moderate or severe hepatic impairment. Refer to Section X for more details.

#### *Rationale for Dose:*

The dosage of bamlanivimab 700 mg and etesevimab 1,400 mg administered together was selected incorporating the following factors:

- Bamlanivimab 4,200 mg has been shown to provide strong evidence of protection against mild or worse COVID-19 compared to placebo in skilled nursing and assisted living facilities.
- Due to the sustained increase in SARS-CoV-2 viral variants circulating in the United States that are resistant to bamlanivimab alone, the

authorization of bamlanivimab alone was revoked on April 16, 2021 (<https://www.fda.gov/media/147629/download>).

- A dosage of bamlanivimab 700 mg and etesevimab 1,400 mg administered together has been shown to reduce COVID-19 related hospitalization (defined as  $\geq 24$  hours of acute care) or death by any cause by Day 29 compared to placebo (treatment rate 0.8%, placebo rate 6%, 87% reduction,  $p < 0.0001$ ).
- A dosage of bamlanivimab 700 mg and etesevimab 1,400 mg is expected to provide near-maximal antiviral activity over the necessary duration for post-exposure prophylaxis.
- A dosage of bamlanivimab 700 mg and etesevimab 1,400 mg is expected to have antiviral activity against the wild-type, B.1.1.7 (Alpha; UK origin), B.1.427/429 (Epsilon; USA [California] origin), B.1.526 (Iota; USA [New York] origin), and B.1.617.1 (Kappa; India origin), B.1.617.2 and sublineage AY.3 (Delta, India origin) viruses, based on available clinical and pseudotyped virus-like (VLP) particle assay, and authentic virus data. Due to a large reduction of pseudotyped VLP neutralization activity, it is unlikely that bamlanivimab 700 mg and etesevimab 1,400 mg will be active against B.1.351 (Beta; South Africa origin), P.1 (Gamma; Brazil origin), and B.1.617.2 sublineages AY.1/AY.2 (commonly known as “Delta plus”; India origin) and B.1.621 (Mu; Colombia origin).

Based on analyses of the available data, the authorized dosage of bamlanivimab 700 mg and etesevimab 1,400 mg, administered together, is expected to have a similar preventative effect to a dosage of bamlanivimab 4,200 mg, administered alone, that was used in the clinical prevention trial, PYAD.

#### IV. Product Information (Dose Preparation and Administration)

##### Preparation

Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile prefilled infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1** and **Table 2**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.

- Remove 1 bamlanivimab vial and 2 etesevimab 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.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 1** or **Table 2**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

### Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set.
  - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1 for patients weighing ≥50 kg** or **Table 2 for patients weighing <50 kg**). 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 bamlanivimab and etesevimab injection with IV solutions and

medications other than 0.9% Sodium Chloride Injection is not known.

- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

**Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion<sup>a</sup> in Patients Weighing 50 kg or More**

Drug <sup>a</sup> : Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Maximum Infusion Rate	Minimum Infusion Time
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL	310 mL/hr	60 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

**Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing Less Than 50 kg**

Drug <sup>a</sup> : Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total 60 mL to an infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Maximum Infusion Rate	Minimum Infusion Time
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL <sup>b</sup>	266 mL/hr	70 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

<sup>b</sup> The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

## **BAMLANIVIMAB AND ETESEVIMAB MUST BE ADMINISTERED TOGETHER.**

### *Bamlanivimab*

Bamlanivimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

### *Etesevimab*

Etesevimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

Bamlanivimab and etesevimab are supplied as:

<b>Antibody</b>	<b>Concentration</b>	<b>Package Size</b>	<b>NDC</b>
Bamlanivimab	700 mg/20 mL (35 mg/mL)	one vial per carton	0002-7910-01
Etesevimab	700 mg/20 mL (35 mg/mL)	one vial per carton	0002-7950-01

## **Storage and Handling**

Bamlanivimab is preservative-free. Discard unused portion.

Etesevimab is preservative-free. Discard unused portion.

Store unopened 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, SHAKE, OR 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 infusion solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours and at room temperature (20°C to 25°C [68°F to 77°F]) and for up to 7 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature prior to administration.

## **V. Background Information on the Disease/Condition and Available Therapeutic Alternatives**

### **Background Information on the Condition**

The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19).

COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, more than 223 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported globally as of September 10, 2021, including an estimated 4.6 million deaths. As of September 10, 2021, approximately 40 million cases of COVID-19, with more than 654,000 deaths, have been reported in the United States according to CDC.

COVID-19 reported in the United States has disproportionately affected the elderly. While approximately 13% of those infected with COVID-19 have been 65 years of age or older, this has accounted for approximately 79% of total deaths (<https://covid.cdc.gov/covid-data-tracker/#demographics>, accessed on 9/10/2021). These findings are similar to data from China, which indicated >80% of deaths occurred among persons aged  $\geq 60$  years (JAMA. 2020;323(13):1239-1242).

Severe illness, defined as hospitalization, admission to the ICU, intubation or mechanical ventilation or death, can occur in adults of any age with COVID-19. Adults of any age with certain underlying comorbidities or conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes, pregnancy, and immunocompromised states are at increased risk for severe illness from the virus that causes COVID-19. Other medical conditions or factors also make certain individuals at high risk for progression to severe disease (<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>).

The respiratory presentation in adolescents has been similar to that in adults. The disease is typically milder in children, but a small proportion have experienced severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Götzinger et al., 2020).

### Prevention Alternatives

There is no adequate, approved, and available alternative to the emergency use of bamlanivimab and etesevimab administered for use as post-exposure prophylaxis of COVID-19, as described above.

On August 2, 2021, Pfizer-BioNTech COVID-19 vaccine (also known as COMIRNATY) was approved for use by FDA. It is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. This vaccine, originally authorized for emergency use on December 11, 2021, contains nucleoside-modified messenger RNA encoding the spike glycoprotein of SARS-CoV-2 and is administered intramuscularly as a series of two doses 3 weeks apart. On May 10, 2021, the Pfizer-BioNTech COVID-19

vaccine EUA was expanded to include adolescents 12 years of age through 15 years of age.

There are currently two additional vaccines against COVID-19 that are authorized for emergency use:

- The Moderna COVID-19 vaccine was authorized for active immunization to prevent COVID-19 in individuals 18 years of age and older on December 18, 2020. This vaccine contains nucleoside-modified messenger RNA encoding the pre-fusion stabilized spike glycoprotein of SARS-CoV-2 and is administered intramuscularly as a series of two doses 4 weeks apart.
- The Janssen COVID-19 vaccine was authorized for active immunization to prevent COVID-19 in individuals 18 years of age and older on February 27, 2021. This vaccine is composed of a recombinant, replication-incompetent human adenovirus type 26 vector that expresses the spike protein in a stabilized conformation. This vaccine is administered intramuscularly as a single dose.

COVID-19 vaccination is recommended for everyone 12 years and older for the prevention of COVID-19 in the United States.<sup>10</sup> The Advisory Committee on Immunization Practices (ACIP) has recommended the FDA-approved Pfizer-BioNTech (COMIRNATY) COVID-19 Vaccine for use in persons  $\geq 16$  years. ACIP has also issued interim recommendations for the use of Pfizer-BioNTech COVID-19 vaccine (in persons ages 12 to 15 years), Moderna COVID-19 vaccine (in persons ages  $\geq 18$  years), and Janssen (Johnson & Johnson) COVID-19 vaccine (in persons ages  $\geq 18$  years).

The CDC considers a history of the following to be a contraindication to vaccination with COVID-19 vaccines:

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of the COVID-19 vaccine
- Immediate allergic reaction of any severity to a previous dose or known (diagnosed) allergy to a component of the vaccine.

Individuals with certain conditions, like solid organ transplant recipients for example, are less likely to mount humoral immune responses compared to immunocompetent participants (Boyarsky, et al., 2021). On August 12, 2021, the FDA amended the EUAs for the Pfizer-BioNTech and Moderna COVID-19 vaccines to allow for the use of an additional dose for certain immunocompromised individuals. The CDC now recommends that people with moderately to severely compromised immune systems receive an additional dose of mRNA COVID-19 vaccine at least 28 days after the initial 2 doses.

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<sup>10</sup> <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>

Based on the safety and efficacy demonstrated and the widespread availability of COVID-19 vaccines in the U.S., a Limitation of Authorized Use stating post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19 should be in the Fact Sheet for Health Care Providers. Similar messaging should be provided in the Fact Sheet for Patients, Parents and Caregivers under “what other prevention choices are there?”.

## VI. Related Regulatory Submission(s)

Bamlanivimab and etesevimab have been studied under INDs 150440, 150707, 151193, 151543, and 153935 (Table 3).

Product Quality reviews for EUA 000090 are cross-referenced for detailed product quality data and information, including manufacturing facilities, related to bamlanivimab.

In addition to the above-mentioned cross-referenced submissions, the following related Master Files are referenced for bamlanivimab and etesevimab:

- DMF 21219
  - Procedure for Sterile Operations in Building B103, Indianapolis, IN
  - Holder: Eli Lilly & Company
- DMF (b) (4)
  - SVP Facility
  - Holder: (b) (4)
- DMF 16307
  - Procedure for Sterile Operation (in Lilly France, Fegersheim)
  - Holder: Eli Lilly & Company
- DMF 32544
  - Procedure for Sterile Operations for the Dedicated Monoclonal Antibody Building
  - Holder: Eli Lilly & Company
- DMF (b) (4)
  - Facilities and Equipment Information for (b) (4), Contract Manufacturing Plant in (b) (4)
  - Holder: (b) (4)
- DMF (b) (4)
  - (b) (4)
  - Holder: (b) (4)
- DMF (b) (4)
  - (b) (4)
  - Holder: (b) (4)
- DMF (b) (4)
  - (b) (4)



- Holder: (b) (4)

## **VII. Summary of Clinical Data**

The data to support the authorization of bamlanivimab and etesevimab administered together for the prevention of COVID was generated from Trial J2X-MC-PYAD (PYAD; BLAZE-2). Additional data from Phase 1, Phase 2, and Phase 3 clinical trials also supports the authorization (Table 3).

Table 3: All Clinical Trials

Study Number	IND, NDA, or Literature Reference	Type of Study (PK, Efficacy, Safety)	Population (Planned N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
J2W-MC-PYAA	150440	PK, Efficacy, Safety	N = 24  Hospitalized patients with moderate or severe COVID-19	Phase 1, randomized, placebo-controlled, double-blind, sponsor-unblinded, single-ascending dose, first in human trial	Single IV infusion  Cohorts 1-3: 6 received BAM, 2 received placebo Cohort 1 = 700 mg BAM Cohort 2 = 2800 mg BAM Cohort 3 = 7000 mg BAM  Assessments to Day 29; 60- day follow-up	Completed  Enrollment N = 26 Cohort 1: N = 8 Cohort 2: N = 9 Cohort 3: N = 9  Clinical Study Report approved 19 November 2020
J2W-MC-PYAB (BLAZE-1)	150440	Efficacy, Safety	N = 3970  <b>Phase 2</b> Mild to moderate COVID-19  Treatment Arms 1-4 & 6: N = 500 participants plus additional placebo to ensure up to 50 concurrent placebo controls for treatment Arm 6  <b>Phase 3</b> Mild to moderate COVID-19 with at least 1 risk factor for developing severe COVID-19 illness; includes adults and adolescents  Treatment Arms 7 & 8: N = ~500 participants per arm. Approximately 150 participants will be enrolled in treatment arm 8 in parallel with arm 9	Phase 2/3, randomized, double-blind, placebo-controlled trial  Addendum 2 (Arm 22): open label, substudy to evaluate safety and efficacy of BAM and ETE in patients 0 to ≤17 years. (b) (4)  Addendum 3 (Arm 20 + 21): open label substudy to evaluate safety of 5-min and 3-min IV push of 350 mg BAM + 700 mg	Single IV infusion in Treatment Arms 1-15, 18 and 20-21; single subcutaneous administration in Arm 19  <b>Phase 2:</b> <ul style="list-style-type: none"><li>Arm 1: Placebo, ~100 concurrent with Arms 2 and 3; 50 concurrent with Arm 6</li><li>Arm 2: 700 mg BAM</li><li>Arm 3: 2800 mg BAM</li><li>Arm 4: 7000 mg BAM</li><li>Arm 6: 2800 mg BAM + 2800 mg ETE</li></ul>	Phase 2 active, closed to enrollment; Phase 3 active, closed to enrollment; Addendum 2 enrolling; Addendum 3, active, closed to enrollment  Enrollment N = 3293  <b>Phase 2:</b> N = 592 <sup>a</sup> ; 577 received trial medication Arm 1: N = 156 Arm 2: N = 101 Arm 3: N = 107 Arm 4: N = 101 Arm 6: N = 112

			<p>Treatment Arm 9: N = ~ 500 participants</p> <p>Treatment Arms 13 and 14: N = 160 for placebo, N = 240 for BAM + ETE</p> <p>Treatment Arm 18: N = ~460 participants</p> <p>Treatment Arm 19: N = ~460 participants</p> <p>Treatment Arm 20 and 21: ~300 participants</p> <p>Treatment Arm 22: N = ~85 participants ages 0 to ≤17 years using weight-based dosing</p>	ETE in adults and adolescents	<p><b>Phase 3:</b></p> <ul style="list-style-type: none"> <li>Arm 7: 2800 mg BAM + 2800 mg ETE</li> <li>Arm 8: Placebo, concurrent with Arms 7 and 9</li> <li>Arm 9: 700 mg BAM + 1400 mg ETE</li> <li>Arm 13: Placebo</li> <li>Arm 14: 350 mg BAM + ETE 700 mg</li> <li>Arm 18: 700 mg BAM + 1400 mg ETE</li> <li>Arm 19: 250 mg BAM + 500 mg ETE</li> </ul> <p>(b) (4)</p> <p><b>Addendum 3:</b></p> <ul style="list-style-type: none"> <li>Arm 20: 350 mg BAM + 700 mg ETE 5-min IV push</li> <li>Arm 21: 350 mg BAM + 700 mg ETE 3-min IV push</li> </ul> <p>Assessments to Day 29; 85- day follow-up</p>	<p><b>Phase 3:</b> N = 1035 Arm 7: 518 Arm 8: 517</p> <p>Arm 8 in parallel with Arm 9 N = 770 Arm 8: 259 Arm 9: 511</p> <p>Arms 13 and 14 N = 314 Arm 13: Blinded Arm 14: Blinded</p> <p>Adolescents: Randomized in Treatment Arms 7-9, 13 and 14 N = 32</p> <p>(b) (4)</p> <p>Addendum 3 Arm 20: N = 30 Arm 21: N = 274</p>
J2X-MC-PYAD (BLAZE-2)	150440	Efficacy, Safety	<p>N = ≤5000 (maximum sample size) Residents and staff of skilled nursing or assisted living facilities; Prevention and treatment cohorts</p> <p><b>Part 1</b> - up to 1700</p>	Phase 3, randomized, double-blind, placebo-controlled study	<p>Single IV infusion</p> <p><b>Part 1:</b></p> <ul style="list-style-type: none"> <li>Arm 1: 4200 mg BAM</li> <li>Arm 2: Placebo</li> </ul>	<p>Part 1, active, enrollment complete; Part 3 active, enrollment complete. Part 2 cancelled.</p> <p>Enrollment</p>

			<p>participants</p> <p><b>Part 2</b> - up to 2000 participants</p> <p><b>Part 3</b> - up to 500 participants</p> <p>The maximum sample size for this trial is approximately 5000 participants in the ITT population.</p>	<p><b>Part 1:</b> goal of achieving ~33 events (in each of the primary and key secondary endpoints) in the prevention population</p> <p><b>Part 2:</b> goal of achieving ~56 events on each of the primary and key secondary endpoints in the Prevention Cohort</p> <p><b>Part 3:</b> considered exploratory and is not powered for inference between the two treatment arms</p>	<p><b>Part 2:</b> <u>Prevention Cohort</u></p> <ul style="list-style-type: none"> <li>Arm 3: 700 mg BAM</li> <li>Arm 4: 350 mg BAM + 700 mg ETE</li> <li>Arm 5: Placebo</li> </ul> <p>Evaluation period of 8 weeks; 169-day follow-up</p> <p><u>Treatment Cohort:</u></p> <ul style="list-style-type: none"> <li>Arm 6: 700 mg BAM</li> <li>Arm 7: 700 mg BAM + 1400 mg ETE</li> </ul> <p>Evaluation period of 8 weeks; 85-day follow-up</p> <p><b>Part 3:</b></p> <ul style="list-style-type: none"> <li>Arm 8: 700 mg BAM</li> <li>Arm 9: 700 mg BAM + 1400 mg ETE</li> </ul> <p>Evaluation period of 4 weeks; 85-day follow-up</p>	<p><b>Part 1:</b> N = 1299 Arm 1: 588 Arm 2: 587</p> <p><b>Part 2:</b> Cancelled</p> <p><b>Part 3:</b> N = 275 consented; 196 infused</p>
J2X-MC-PYAG	150440	PK, Safety	N = 27 Healthy volunteers	Phase 1, randomized, placebo-controlled, participant- and investigator-blind, (b) (4), PK trial	(b) (4)	<p>Completed</p> <p>Enrollment N = 25</p> <p>Cohort 1: N = 9 Cohort 2: N = 9 Cohort 3: N = 7</p>

					(b) (4)	
J2X-MC-PYAH (BLAZE-4)	150440	Efficacy, Safety	N = 1416 Mild to moderate COVID-19  Addendum 2 N = 66	Phase 2, placebo-controlled, double-blind, randomized, single-dose trial in participants with mild-to-moderate COVID-19 illness  Treatment Arms 1-5 were in parallel  Arms 1-3 continued and were in parallel with Arm 6  Treatment Arms 7 and 8: in parallel with each other  Treatment Arms 9-11: double blind, low risk participants  Treatment Arms 12 and 13: high risk participants randomized 2:1, parallel and open label  Treatment Arm 14: high risk participants, open-label, to enroll following completion of enrollment in Arms 12 and 13  Addendum 2: Open-label substudy to explore accelerated IV administration of BAM alone and with ETE  (b) (4)	Single IV infusion; Arm B SC administration  • Arm 1: Placebo (b) (4) • (b) (4) • Arm 3: 700 mg BAM + 1400 mg ETE • Arm 4: 2800 mg BAM + 2800 mg ETE • Arm 5: 700 mg BAM • (b) (4) • (b) (4) • Arm 8: Placebo (b) (4) • (b) (4) • Arm 11: Placebo (b) (4) • (b) (4) • (b) (4)  Addendum 2: • Arm A: 700 mg BAM • Arm B: 700 mg BAM + 1400 mg ETE	Arms 1-8, Addendum 2: Active, enrollment complete  Enrollment N = 719 Arms 1-6: Arm 1: N = 153 Arm 2: N = 103 Arm 3: N = 158 Arm 4: N = 101 Arm 5: N = 103 Arm 6: N = 101  Arms 7 and 8: N = 202 Arm 7: 101 Arm 8: 101  Arms 9-14 N = 715  Arms 9-11: N = 385 Arm 9: Blinded Arm 10: Blinded Arm 11: Blinded  Arms 12-13: N = 151  Arms 12-14: Open-label Arm 14: N = 179  Addendum 2 N = 66  (b) (4)

				(b) (4)	(b) (4)	
J2Z-MC-PGAA	150707	PK, safety	N = ≤ 30 Healthy volunteers	Phase 1, randomized, placebo-controlled trial	Single IV administration  Cohorts 1 and 2: 7 received ETE, 2 received placebo  Cohort 3: 6 received ETE, 2 received placebo <ul style="list-style-type: none"><li>Cohort 1 = 700 mg ETE</li><li>Cohort 2 = 2800 mg ETE</li><li>Cohort 3 = 7000 mg ETE</li></ul>	Completed  Enrollment N = 26  Cohort 1: N = 9 Cohort 2: N = 9 Cohort 3: N = 8  Clinical Study Report approved 01 December 2020

					85-day follow-up	
J2Z-MC-PGAB	150707	PK, safety	N = ≤ 22 Healthy volunteers	Phase 1, randomized, placebo-controlled trial	(b) (4)	Completed  Enrollment N = 18  Cohort 1: N = 9 Cohort 2: N = 9
J2X-MC-PYAJ (BLAZE-5)	150440	Efficacy, safety	Study Participants: N = 3000 adults and children (≥12 years) infected with SARS-CoV-2, at high risk of developing severe disease requiring hospitalization  Matched Controls: N = 3000 NM Health System members that test positive for COVID-19	Open label, single arm, prospective, cohort study, using matched real-world external controls (no placebo arm)	Study participants will receive single IV infusion of 700 mg BAM  Follow-up on Days 2, 29, 60, 90	Active, enrollment closed early (31 March 2021) due to enrollment challenges N = 109
JS016-001-I	NA <sup>p</sup>	PK, safety	N = 40 Healthy Chinese volunteers	Phase 1, randomized, double-blind, placebo-controlled trial	Single IV administration  Cohorts 1: 3 received ETE, 1 received placebo  Cohorts 2-4: 9 received ETE, 3 received placebo <ul style="list-style-type: none"><li>Cohort 1 = 2.5 mg/kg ETE</li><li>Cohort 2 = 10 mg/kg ETE</li><li>Cohort 3 = 25 mg/kg ETE</li><li>Cohort 4 = 50 mg/kg ETE</li></ul> 85-day follow-up	(b) (4)

JS016-002-Ib/II	NA <sup>p</sup>	PK, safety	<p>N = 90</p> <p>Participants with mild and moderate COVID-19 or SARS-CoV-2 asymptomatic infection</p> <p>30 participants per cohort; randomized 2:1 treatment to placebo</p>	Phase 1b/2, randomized, double blinded, placebo-controlled study	<p>Single IV infusion</p> <ul style="list-style-type: none"><li>Cohort 1 = 25 mg/kg ETE</li><li>Cohort 2 = 50 mg/kg ETE</li><li>Cohort 3 = 100 mg/kg ETE</li></ul> <p>85-day follow-up</p>	(b) (4)
ACTIV-2	151193	Efficacy, safety	<p>N = 220 for Phase 2</p> <p>N = 1000 per arm for Phase 3, inclusive of the patients enrolled in the Phase 2 portion of the trial</p> <p>Outpatient adults positive for SARS- CoV-2</p>	Phase 2/3, randomized, blinded, controlled, platform trial	<p>Single IV infusion</p> <p><b>Phase 2:</b></p> <ul style="list-style-type: none"><li>Arm 1: Placebo</li><li>Arm 2: 7000 mg BAM initially, dose then changed to 700 mg BAM</li></ul> <p><b>Phase 3:</b></p> <ul style="list-style-type: none"><li>Arm 1: Placebo</li><li>Arm 2: 700 mg BAM</li></ul> <p>28 days of intensive follow-up, followed by limited follow-up through 24 weeks</p>	(b) (4)
ACTIV-3	151543	Efficacy, Safety	<p>N = 1000</p> <p><b>Stage 1</b> N= 150 participants per IA/placebo: Inpatient adults with COVID-19 symptoms, without end organ failure</p> <p><b>Stage 2</b> N = 500 participants per IA/ placebo (including those from Stage 1)</p>	Phase 3, randomized, blinded, controlled platform study with 2 stages	<p>Single IV infusion</p> <p><b>Stage 1:</b></p> <ul style="list-style-type: none"><li>Arm 1: Placebo</li><li>Arm 2: 7000 mg BAM</li></ul> <p>Follow-up 90 days</p>	(b) (4)
2020-0081	153935	Efficacy, Safety	Study Participants N = 7500	Open label, single-	Study participants	(b) (4)



			<p>UHC members (≥65 years) deemed at high risk of contracting COVID-19</p> <p>Matched Controls N = 7500</p> <p>UHC members (≥65 years) that seek care at an Optum Care facility for confirmed symptomatic COVID-19</p>	<p>arm, pragmatic, observational study using matched, real-world external controls (no placebo arm)</p>	<p>will receive 700 mg BAM</p> <p>Infusions to be administered at home by an Optum Infusion Nurse</p> <p>Follow-up 18 days; up to 6 months of symptom tracking post-infusion</p> <p>Matched controls will be followed for up to 38 after symptom onset</p>	<p>(b) (4)</p>
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Source: Adapted from Applicant Submission to EUA dated September 2, 2021 entitled “Updated Table of Clinical Studies.

Abbreviations: BAM = bamlanivimab/LY3819253/LY-CoV555, BLA = biologics license application; COVID-19 = coronavirus disease 2019; DBL = database lock; DSMB = Data Safety Monitoring Board; Enrolled = entered and randomized; ETE = etesevimab/LY3832479/LY-CoV016, IND = investigational new drug; ITT = intention to treat; IV = intravenous; (b) (4) ; N = number of participants; NDA = new drug application; NIAID = National Institute of Allergy and Infectious Diseases; NM = new Mexico, PK = pharmacokinetics; SC = subcutaneous; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UHC = UnitedHealthcare.

<sup>a</sup> 592 participants were enrolled (i.e., entered and randomized) in Arms 1 to 4 and Arm 6. Of those 592 enrolled participants, 15 were not infused with trial drug.

<sup>b</sup> Not applicable. Trial sponsored by Junshi Biosciences in China and not under a US IND.

UHC members may be used as members of the control population based on electronic medical record review and matching to enrolled participants

## VIII. Human Clinical Efficacy

The source of clinical efficacy for assessing post-exposure prophylaxis was Trial PYAD (also called BLAZE-2). This was a randomized, double-blind, placebo-controlled trial in residents and staff of skilled nursing and assisted living facilities.

The data supporting this EUA were from Part 1 of the trial, which randomized participants in a 1:1 ratio to a single intravenous infusion of bamlanivimab 4200 mg or matching placebo. Because study drug was administered after index cases were identified at facilities, but before diagnostic results from pre-randomization samples were available, participants in this trial were classified as being in a Prevention Population or Treatment Population depending on whether they were later determined to have been infected at baseline<sup>1</sup>. The efficacy data from Trial PYAD discussed in this review are based on the Prevention Population. No data were collected on the type or extent of exposure to the index case. Contact tracing was not conducted to identify whether the study participants who enrolled in Trial PYAD were, in fact, the index case that triggered enrollment at the facility. However, study site personnel excluded all known positive cases and only enrolled patients who did not have a confirmed positive SARS-CoV-2 test. In addition, facility staff who tested positive for SARS-CoV-2 would have been restricted from returning to work, and therefore could not have received study drug.

The main inclusion criteria specified that participants were to be residents or staff at least 18 years old or older in skilled nursing or assisted living facilities with at least one confirmed case of SARS-CoV-2 detected  $\leq 7$  days prior to randomization. The main exclusion criteria disallowed previous known SARS-CoV-2 infection, receipt of monoclonal antibodies or vaccines for COVID-19, pregnancy, or serious concomitant systemic diseases. Block randomization within each facility stratified by role (resident or staff) and sex.

There was an 8 week evaluation period after treatment. Study visits were scheduled on Days 1-7 and then weekly until Day 57. At these visits, participants were assessed for adverse events, concomitant medications, vital signs, hospitalization events, clinical signs and symptoms (from a questionnaire concerning symptoms occurring in the past 24 hours), SARS-CoV-2 nasal swabs for PCR testing, and additional evaluations.

The primary endpoint for the Prevention Population was cumulative incidence of COVID-19, defined as the detection of SARS-CoV-2 by RT-PCR AND mild or

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<sup>1</sup> The Prevention Population is defined as all enrolled participants who were SARS-CoV-2 RT-PCR negative and SARS-CoV-2 serology negative at baseline. The Treatment Population is defined as all enrolled participants in Part 1 who were SARS-CoV-2 RT-PCR positive at baseline and SARS-CoV-2 serology negative. Enrolled participants who were SARS-CoV-2 serology positive at baseline were considered to be in the Serology Positive Population.

worse disease severity within 21 days of detection, up to 8 weeks after randomization. Severity levels were as defined in the table below.

**Table 4: Definitions for COVID-19 Severity**

Severity	Description
Mild	<p>Mild symptoms that could include</p> <ul style="list-style-type: none"> <li>Fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea</li> </ul> <p>AND</p> <p>No clinical signs indicative of Moderate, Severe, or Critical Severity</p>
Moderate	<p>Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion</p> <p>AND</p> <p>Clinical signs suggestive of moderate illness with COVID-19, such as:</p> <ul style="list-style-type: none"> <li>Respiratory rate <math>\geq 20</math> breaths per minute</li> <li>Heart rate <math>\geq 90</math> beats per minute</li> <li>Oxygen utilization increase of <math>\geq 1</math> liter per minute (for participants receiving oxygen at baseline)</li> <li>IV fluid initiation</li> </ul> <p>AND</p> <p>No clinical signs indicative of Severe or Critical Illness Severity</p>
Severe	<p>Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress</p> <p>AND</p> <p>Clinical signs indicative of severe systemic illness with COVID-19, such as</p> <ul style="list-style-type: none"> <li>Respiratory rate <math>\geq 30</math> breaths per minute,</li> <li>Heart rate <math>\geq 125</math> beats per minute,</li> <li>SpO<sub>2</sub> <math>\leq 93\%</math> on room air at sea level or PaO<sub>2</sub>/FiO<sub>2</sub> <math>&lt; 300</math></li> </ul> <p>AND</p> <p>No clinical signs indicative of Critical Illness Severity</p>
Critical	<p>Evidence of critical illness, defined by at least one of the following:</p> <ul style="list-style-type: none"> <li>Respiratory failure defined based on resource utilization requiring at least one of the following: <ul style="list-style-type: none"> <li>Endotracheal intubation and mechanical ventilation,</li> <li>Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates <math>&gt; 20</math> L/min with fraction of delivered oxygen <math>\geq 0.5</math>),</li> <li>Noninvasive positive pressure ventilation,</li> <li>Extracorporeal membrane oxygenation (ECMO), or</li> <li>Clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)</li> </ul> </li> <li>Shock</li> <li>Multi-organ dysfunction/failure</li> </ul>
Death	

Source: Trial PYAD protocol amendment c, Table 1.

The protocol specified two key secondary endpoints. The first was cumulative incidence of moderate or worse severity COVID-19, defined as the detection of SARS-CoV-2 by RT-PCR AND moderate or worse disease severity within 21

days of detection, up to 8 weeks after randomization. As noted in the above table, moderate severity disease required shortness of breath with exertion and clinical signs in addition to the symptoms used to define mild disease.

The second key secondary endpoint was cumulative incidence of SARS-CoV-2, defined as the detection of SARS-CoV-2 by RT-PCR within 4 weeks of randomization. An additional secondary endpoint was incidence of infection within 8 weeks of infection.

Efficacy analyses for Trial PYAD Part 1 were conducted in the Prevention Population. This was defined as all randomized participants who were SARS-CoV-2 RT-PCR negative and serology negative at baseline. The primary and secondary analyses excluded 1 participant in the placebo group and 4 participants in the bamlanivimab arm who did not have any post-baseline RT-PCR tests performed.

Analyses of the primary and key secondary endpoints were based on logistic regression. The logistic models adjusted for facility, role within facility (resident or staff), and sex. P-values were computed using the Rao score test.

The statistical analysis plan prespecified exploratory subgroup analyses of primary and key secondary endpoints by role within the facility, age, and sex. The Applicant has additionally reported results in post-hoc subgroups of (i) participants at high risk of disease progression; (ii) immunocompromised participants. High risk participants included all facility residents and facility staff meeting at least of the following criteria: age  $\geq 65$  years; BMI  $\geq 35$ ; diabetes; immunosuppressive disease; immunosuppressive treatment; age  $\geq 55$  years and at least one of cardiovascular disease, hypertension, or COPD or another chronic respiratory disease. The immunocompromised subgroup was defined by immunosuppressive disease, immunosuppressive treatment, or age  $\geq 75$  years.

Trial PYAD Part 1 was designed as an event driven study that would enroll until at least 300 residents were recruited and 33 participants had events for moderate or worse severity COVID-19. The Applicant calculated that this would provide 90% power to detect a treatment effect for primary or key secondary endpoints assuming a standard two-sided 0.05 significance level, a 4% event rate in the placebo arm, and a risk ratio of 0.33 for the bamlanivimab arm versus the placebo arm. The Applicant anticipated that approximately 1300 participants in the Prevention Population would be needed to achieve the requisite number of events.

The primary analysis for Trial PYAD Part 1 was to be based on a database lock triggered by reaching the target number of events for this event driven trial. However, to account for participants still undergoing follow-up the statistical analysis plan also specified an additional database lock to occur after all participants completed the 8 week evaluation period or withdrew from the study.

Participants and investigators were to remain blinded to treatment assignments until participants had completed this follow-up evaluation period. Results provided by the Applicant and discussed in this review are based on the database lock after the end of the follow-up period rather than primary analysis database lock. This was acceptable because this second database lock was prespecified and encompassed more complete follow-up data, and results described below would be robust to multiplicity corrections stemming from analyses conducted at different calendar times.

The table below displays baseline characteristics in the Prevention Population of Trial PYAD Part 1. Approximately three quarters of participants were female, under 30% were 65 years or older, approximately 90% were White, and all were enrolled in the United States. Approximately 30% of participants were residents of facilities while approximately 70% were staff, approximately 60% were considered at high risk for disease progression, and slightly under 20% were classified by the Applicant as immunocompromised. Baseline characteristics were well balanced between treatment groups. Per the inclusion and exclusion criteria this trial was conducted in unvaccinated participants. Participants in the Prevention Population were enrolled at over 70 facilities, and no facility enrolled more than 4% of total participants.

**Table 5: Baseline Demographics and Disease Characteristics (Trial PYAD, Part 1, Prevention Population)**

	Placebo (N = 482)	Bamlanivimab (N = 484)
Female	367 (76%)	355 (73%)
Age ≥65 years	137 (28%)	145 (30%)
White	429 (90%)	429 (89%)
Black or African American	41 (9%)	38 (8%)
Hispanic or Latino	28 (6%)	20 (4%)
Enrolled in United States	482 (100%)	484 (100%)
Median BMI	30	30
Facility resident	139 (29%)	160 (33%)
Facility staff	343 (71%)	323 (67%)
At high risk	282 (59%)	292 (60%)
Immunocompromised	86 (18%)	98 (20%)

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request Data Appendix, Tables APP.3.4 - APP.3.8.

The following table shows that over 95% of participants completed study assessments. The most common reason for study discontinuation was withdrawal by the participant.

**Table 6: Participant Disposition (Trial PYAD, Part 1, Prevention Population)**

	Placebo (N = 482)	Bamlanivimab (N = 484)
Study disposition		
Discontinued	23 (5%)	20 (4%)
Continuing study	459 (95%)	464 (96%)
Reason for study discontinuation		

Death	6 (1%)	5 (1%)
Loss to follow-up	1 (0.2%)	2 (0.4%)
Other	0 (0%)	1 (0.2%)
Withdrawal by subject	16 (3%)	12 (2%)

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request Data Appendix, Table APP.3.2.

Results for the primary endpoint in the Prevention Population favored bamlanivimab. As shown in the subsequent table, rates of mild or worse severity COVID-19 through Week 8 were 15% in the placebo arm compared with 9% for bamlanivimab. This corresponded to an estimated 40% reduction in event rates and an estimated odds ratio of 0.43 (95% CI: 0.28 to 0.68) and highly statistically significant  $p < 0.001$ . The confidence interval and p-value did not attempt to account for possible dependence in participant outcomes due to spread of infections between participants.

**Table 7: Primary Analysis of Mild or Worse Severity COVID-19 by Week 8 (Trial PYAD, Part 1, Prevention Population)**

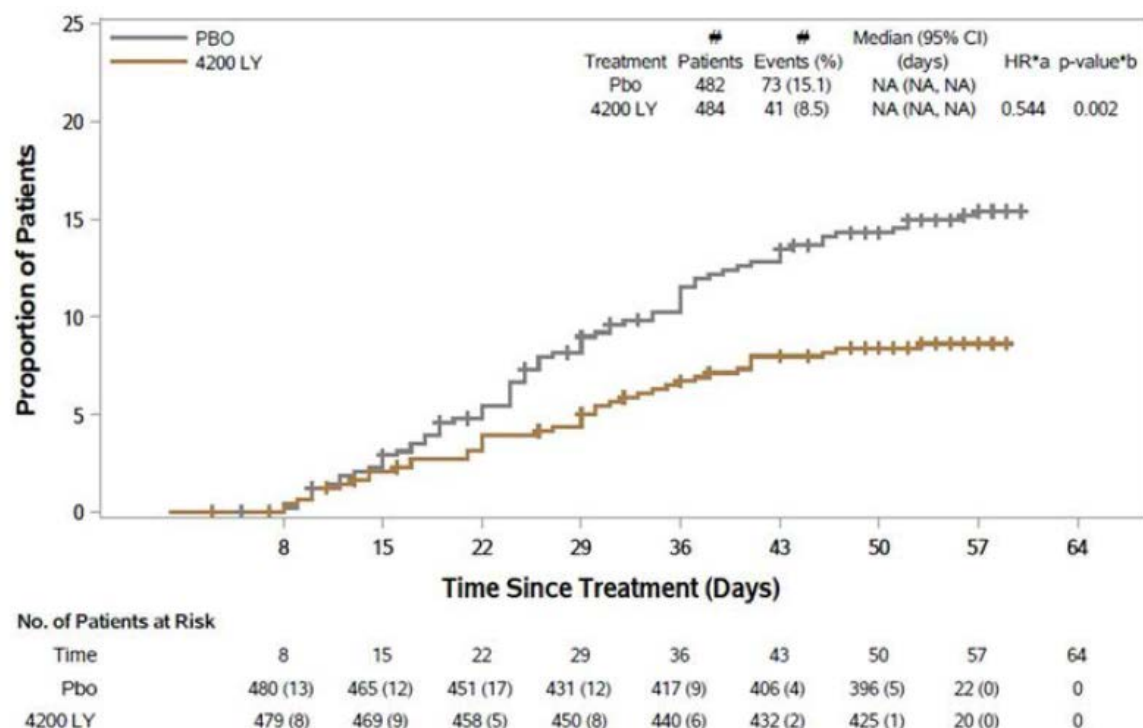
	Incidence		Odds ratio (95% CI) versus placebo	P-value
	Placebo	Bamlanivimab		
Prevention Population	73/481 (15%)	41/480 (9%)	0.43 (0.28 to 0.68)	<0.001

Notes: Incidence denominators are the number of participants with at least 1 post-baseline RT-PCR test. Odds ratio inference is based on logistic regression with covariates of treatment, facility, sex, and role in facility (resident versus staff) as covariates. The p-value is based on a Rao score test.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Table 8.7

The Kaplan-Meier plot below shows that the cumulative incidence curves began separating approximately two weeks after treatment and continued separating through the 8 week follow-up period.

**Figure 1: Time to Mild Severity COVID-19 Symptoms (Trial PYAD, Part 1, Prevention Population)**



Notes: The hazard ratio is based on an unstratified Cox model. The p-value is based on a two-sided logrank test.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Figure 8.1.

The next table shows results for the primary endpoint in baseline subgroups. Bamlanivimab clearly provided a benefit for facility residents in reducing rates of mild or worse severity COVID-19 by Week 8, as rates were 22% in the placebo group compared with only 9% in the bamlanivimab group and the difference was highly significant. There was more uncertainty in the subgroup of facility staff (which included both high risk and low risk staff) as the rates were 12% for placebo compared with 8% for bamlanivimab, and the nominal confidence interval and p-value for the treatment effect in this subgroup were borderline non-significant. By combining residents and high risk staff into a post-hoc high risk subgroup, bamlanivimab led to a clear benefit in the combined group and reduced the placebo event rate by 50%. In the post-hoc subgroup of immunocompromised participants (immunosuppressive disease, immunosuppressive treatment, or age  $\geq 75$  years), the Applicant's results shown in Table 8 suggested benefit. For this group there was a difference between the covariate adjusted odds ratio (0.25) and p-value (0.02) and an unadjusted odds ratio (0.65) and p-value (0.38) from Fisher's exact test, and the Applicant attributed these differences to adjustment for the large number of facilities.

**Table 8: Mild or Worse Severity COVID-19 by Week 8 by Subgroup (Trial PYAD, Part 1, Prevention Population)**

	Incidence		Odds ratio (95% CI) versus placebo	P-value
	Placebo	Bamlanivimab		
Residents	31/138 (22%)	14/158 (9%)	0.20 (0.08 to 0.49)	<0.001
Staff	42/343 (12%)	27/321 (8%)	0.58 (0.33 to 1.02)	0.06
High risk	50/281 (18%)	25/288 (9%)	0.28 (0.15 to 0.53)	<0.001
Immunocompromised	13/86 (15%)	10/96 (10%)	0.25 (0.07 to 0.83)	0.02

Notes: Incidence denominators are the number of participants with at least 1 post-baseline RT-PCR test. Odds ratio inference is based on logistic regression with covariates of treatment, facility, sex, and role in facility (resident versus staff) as covariates. The p-values are based on Rao score tests. High risk participants included all facility residents and facility staff meeting at least of the following criteria: age ≥65 years; BMI ≥35; diabetes; immunosuppressive disease; immunosuppressive treatment; age ≥55 years and at least one of cardiovascular disease, hypertension, or COPD or another chronic respiratory disease. The immunocompromised subgroup was defined by immunosuppressive disease, immunosuppressive treatment, or age ≥75 years.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Tables 8.8-8.9.

Results for the key secondary endpoint of moderate or worse severity COVID-19 by Week 8 were very similar to results for the primary endpoint based on mild or worse severity disease. This was because only 6 participants who were classified as having mild or worse disease were not also classified as developing moderate or worse disease.

**Table 9: Moderate or Worse Severity COVID-19 by Week 8 (Trial PYAD, Part 1, Prevention Population)**

	Incidence		Odds ratio (95% CI) versus placebo	P-value
	Placebo	Bamlanivimab		
Prevention Population	68/481 (14%)	40/480 (8%)	0.46 (0.29 to 0.73)	<0.001
Residents	30/138 (22%)	14/158 (9%)	0.20 (0.08 to 0.49)	<0.001
Staff	38/343 (11%)	26/321 (8%)	0.61 (0.34 to 1.09)	0.09
High risk	48/281 (17%)	25/288 (9%)	0.30 (0.16 to 0.56)	<0.001
Immunocompromised	13/86 (15%)	10/96 (10%)	0.25 (0.07 to 0.83)	0.02

Notes: Incidence denominators are the number of participants with at least 1 post-baseline RT-PCR test. Odds ratio inference is based on logistic regression with covariates of treatment, facility, sex, and role in facility (resident versus staff) as covariates. The p-values are based on a Rao score tests. High risk participants included all facility residents and facility staff meeting at least of the following criteria: age ≥65 years; BMI ≥35; diabetes; immunosuppressive disease; immunosuppressive treatment; age ≥55 years and at least one of cardiovascular disease, hypertension, or COPD or another chronic respiratory disease. The immunocompromised subgroup was defined by immunosuppressive disease, immunosuppressive treatment, or age ≥75 years.



For the other key secondary endpoint of cumulative incidence of SARS-CoV-2 infection by Week 4 the results also favored bamlanivimab. Infection rates in placebo group were 23% in the placebo arm compared with 18% in the bamlanivimab arm, which resulted in a statistically significant difference ( $p = 0.02$ ). Results were more dramatic in the subgroup of facility residents as treatment more than halved the placebo infection rate of 32% to only 15%. There were no trends toward infection reduction in facility staff at Week 4 as event rates were approximately 20% in both the placebo and bamlanivimab arms. Results also favored bamlanivimab in the post-hoc subgroups of high risk participants (combining residents and high risk staff) and immunocompromised participants. For the immunocompromised subgroup the reported covariate adjusted odds ratio (0.17) and p-value ( $p=0.001$ ) greatly differed from the unadjusted odds ratio (0.62) and p-value (0.20) based on Fisher's exact test, and the Applicant stated this was due to adjustment for the large number of facilities. SARS-CoV-2 infection results at Week 8 continued to support bamlanivimab. The main difference from the Week 4 results was that trends now also favored bamlanivimab for facility staff in addition to residents.

**Table 10: Cumulative Incidence of SARS-CoV-2 Infection (Trial PYAD, Part 1, Prevention Population)**

	Incidence by Week 4		Odds ratio (95% CI) versus placebo	P-value
	Placebo	Bamlanivimab		
Prevention Population	112/481 (23%)	86/480 (18%)	0.66 (0.46 to 0.94)	0.02
Residents	44/138 (32%)	23/158 (15%)	0.23 (0.11 to 0.48)	<0.001
Staff	68/343 (20%)	62/321 (19%)	0.96 (0.62 to 1.49)	0.87
High risk	74/281 (26%)	50/288 (17%)	0.51 (0.31 to 0.83)	<0.01
Immunocompromised	21/86 (24%)	16/96 (17%)	0.17 (0.05 to 0.53)	0.001
	Incidence by Week 8		Odds ratio (95% CI) versus placebo	P-value
	Placebo	Bamlanivimab		
Prevention Population	168/481 (35%)	114/480 (24%)	0.51 (0.37 to 0.70)	<0.001
Residents	56/138 (41%)	33/158 (21%)	0.21 (0.10 to 0.42)	<0.001
Staff	112/343 (33%)	80/321 (25%)	0.66 (0.45 to 0.97)	0.03
High risk	100/281 (36%)	67/292 (23%)	0.46 (0.29 to 0.72)	<0.001
Immunocompromised	30/86 (35%)	22/96 (23%)	0.17 (0.06 to 0.47)	<0.001

Notes: Incidence denominators are the number of participants with at least 1 post-baseline RT-PCR test. Odds ratio inference is based on logistic regression with covariates of treatment, facility, sex, and role in facility (resident versus staff) as covariates. The p-values are based on a Rao score tests. High risk participants included all facility residents and facility staff meeting at least of the following criteria: age  $\geq 65$  years; BMI  $\geq 35$ ; diabetes; immunosuppressive disease; immunosuppressive treatment; age  $\geq 55$  years and at least one of cardiovascular disease, hypertension, or COPD or another chronic respiratory disease. The immunocompromised subgroup was defined by immunosuppressive disease, immunosuppressive treatment, or age  $\geq 75$  years.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Tables 8.13-8.22.

This trial was not powered to assess treatment effects on mortality. Facility residents may have a high underlying risk of death independent of COVID-19. In the Prevention Population there were 6 deaths in the placebo group compared with 5 deaths in the bamlanivimab group, but all 4 deaths attributed to COVID-19 were in the placebo arm. Full narratives for deaths attributed to COVID-19 within the Prevention Population were reviewed and the Division concurred with the adjudication.

Overall, Trial PYAD Part 1 provided strong evidence that bamlanivimab prevented COVID-19 in skilled nursing and assisted living facilities. Results for the primary endpoint were highly statistically significant and corresponded to an estimated 40% reduction in rates of mild or worse severity COVID-19 through Week 8 in the overall Prevention Population that included both low and high risk participants. Results for a key secondary endpoint also suggested that bamlanivimab reduced rates of SARS-CoV-2 infection, and thus may limit further spread when deployed. The strongest evidence of benefit was in facility residents as well as a high risk subgroup that combined both residents and high risk facility staff. This high risk subgroup demonstrated a 70% reduction in risk of moderate or worse severity of COVID-19 by Week 8. The main limitation of Trial PYAD Part 1 was that it only provided clinical evidence of benefit for a single 4200 mg dose of bamlanivimab alone. Thus, justification for the proposed population and dosing regimen for the post-exposure prophylaxis authorization is discussed in Section XI.

## **IX. Human Clinical Safety**

Data to support a post-exposure prophylaxis use was generated from Trial PYAD, where participants were randomized to receive bamlanivimab 4,200 mg or placebo. Since the completion of this trial, the emergency use authorization of bamlanivimab alone (EUA 90) was revoked due to the increased frequency of resistant SARS-CoV-2 variants circulating in the US. It is therefore not appropriate to use bamlanivimab alone for the treatment or prevention of COVID-19. Given that bamlanivimab and etesevimab together have activity against the variants currently circulating in the United States (see below, *Antiviral Resistance*) and considering the results from PYAD, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective as post-exposure prophylaxis of COVID-19 infection.

Bamlanivimab and etesevimab administered together have only been studied for treatment of COVID-19. Based on the efficacy and safety data for bamlanivimab and etesevimab for treatment, it is reasonable to consider bamlanivimab and etesevimab for the post-exposure prophylaxis of COVID-19 infection without conducting an additional clinical trial.

Bamlanivimab 700 mg and etesevimab 1,400 mg are authorized for emergency use 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 progression to severe COVID-19, including hospitalization and death. The safety of bamlanivimab and etesevimab administered together as treatment is based on an exposure of approximately 1,400 clinical trial participants who received bamlanivimab and etesevimab at the authorized dose or higher in BLAZE-1 and BLAZE-4.

As stated in the EUA 94 Fact Sheet for Health Care Providers, anaphylaxis (n=1, 0.07%) and infusion related reactions (n=16, 1.1%) were considered rare adverse reactions. In the case of anaphylaxis and serious infusion-related reactions, all infusions were stopped, and treatment was administered. One case required epinephrine. All events resolved. Clinical worsening of COVID-19 after administration of bamlanivimab as treatment has been reported, but it is not known if this is related to bamlanivimab use or due to progression of COVID-19.

The most common treatment-emergent adverse events in the bamlanivimab and etesevimab treatment group in BLAZE-1 and BLAZE-4 included nausea, dizziness, and pruritus. No treatment-emergent adverse events occurred in more than 1% of participants and the rates were comparable in the treatment and placebo groups. In general, bamlanivimab and etesevimab have been well tolerated when used for the treatment of mild to moderate COVID-19 in individuals that are at higher risk for disease progression.

Given that new safety signals were not identified for bamlanivimab during the conduct of PYAD, it is likely that the safety profile for treatment with bamlanivimab and etesevimab would be similar when these monoclonals are used for post-exposure prophylaxis.

### Trial PYAD – Safety Results

#### *Exposure for Safety Analysis*

The safety population in Trial PYAD is comprised of 1175 participants (n = 966 in the Prevention Population, n = 132 in the Treatment Population, and n = 77 in

the Serology Positive Population<sup>1</sup>). The reviewed safety data reflects a database lock from January 13, 2021. Clinical events related to COVID- 19, including deaths and SAEs, were exempt from AE reporting unless the investigator deemed the event was related to the administration of trial treatment.

### Adverse Events

Treatment-emergent adverse events (AEs) were comparable across the placebo and bamlanivimab cohorts. The majority of AEs were mild in severity using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017). There were 6 non-COVID related deaths in the placebo group, compared to 5 in the bamlanivimab cohort (Table 11).

**Table 11: Summary of Adverse Events, Safety Population, Trial PYAD**

	Placebo (N = 587) n (%)	Bamlanivimab (N = 588) n (%)
TEAEs <sup>a</sup>	111 (19%)	118 (20%)
TEAEs by severity <sup>a,b</sup>		
Mild	61 (10%)	66 (11%)
Moderate	31 (5%)	29 (5%)
Severe	17 (3%)	19 (3%)
Missing	2 (<1%)	4 (1%)
Deaths due to AEs <sup>c,d</sup>	6 (1%)	5 (1%)
SAEs	19 (3%)	22 (4%)
Discontinuations from study participation due to AEs, including death <sup>d</sup>	6 (1%)	5 (1%)

Abbreviations: AE = adverse event, Bamlanivimab = 4200 mg bamlanivimab; COVID-19 = coronavirus disease 2019; n = number of participants in the selected category; N – number of participants in the Safety Population; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

<sup>a</sup>A TEAE is defined as an event that first occurred or worsened in severity after baseline.

<sup>b</sup>Patients with multiple occurrences of the same event are counted under the highest severity

<sup>c</sup>Does not include death related to COVID-19, as they are captured as study outcome

<sup>d</sup>Per protocol, there was no provision for discontinuing participant evaluation and follow-up due to AEs. Therefore, all discontinuations due to AEs reflect death due to AEs.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Table 8.26

Adverse event rates were similar in the Prevention Population (Table 12) and when considering specific subgroups within the Prevention Population (residents, Table 13; high risk participants, Table 14; immunocompromised participants, Table 15).

<sup>1</sup> The Prevention Population is defined as all enrolled participants who were SARS-CoV-2 RT-PCR negative and SARS-CoV-2 serology negative at baseline. The Treatment Population is defined as all enrolled participants in Part 1 who were SARS-CoV-2 RT-PCR positive at baseline and SARS-CoV-2 serology negative. Enrolled participants who were SARS-CoV-2 serology positive at baseline were considered to be in the Serology Positive Population.

**Table 12: Summary of Adverse Events, Prevention Population, Trial PYAD**

	Placebo (N = 482) n (%)	Bamlanivimab (N = 484) n (%)
TEAEs <sup>a</sup>	86 (18%)	97 (20%)
TEAEs by severity <sup>a,b</sup>		
Mild	49 (10%)	54 (11%)
Moderate	24 (5%)	25 (5%)
Severe	12 (3%)	15 (3%)
Missing	1 (<1%)	3 (1%)
Deaths due to AEs <sup>c,d</sup>	2 (<1%)	5 (1%)
SAEs	13 (3%)	19 (4%)
Discontinuations from study participation due to AEs, including death <sup>d</sup>	2 (<1%)	5 (1%)

Abbreviations: AE = adverse event, Bamlanivimab = 4200 mg bamlanivimab; COVID-19 = coronavirus disease 2019; n = number of participants in the selected category; N – number of participants in the Safety Population; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

<sup>a</sup>A TEAE is defined as an event that first occurred or worsened in severity after baseline.

<sup>b</sup>Patients with multiple occurrences of the same event are counted under the highest severity

<sup>c</sup>Does not include death related to COVID-19, as they are captured as study outcome

<sup>d</sup>Per protocol, there was no provision for discontinuing participant evaluation and follow-up due to AEs. Therefore, all discontinuations due to AEs reflect death due to AEs.

Source: Regulatory Response dated May 17, 2021, Table 5.1

**Table 13: Summary of Adverse Events, Residents in Prevention Population, Trial PYAD**

	Placebo (N = 139) n (%)	Bamlanivimab (N = 160) n (%)
TEAEs <sup>a</sup>	30 (22%)	29 (18%)
TEAEs by severity <sup>a,b</sup>		
Mild	15 (11%)	10 (6%)
Moderate	6 (4%)	8 (5%)
Severe	8 (6%)	10 (6%)
Missing	1 (1%)	1 (1%)
Deaths due to AEs <sup>c,d</sup>	2 (1%)	5 (3%) <sup>e</sup>
SAEs	10 (7%)	14 (9%)
Discontinuations from study participation due to AEs, including death <sup>d</sup>	2 (1%)	5 (3%)

Abbreviations: AE = adverse event, Bamlanivimab = 4200 mg bamlanivimab; COVID-19 = coronavirus disease 2019; n = number of participants in the selected category; N – number of participants in the Safety Population; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

<sup>a</sup>A TEAE is defined as an event that first occurred or worsened in severity after baseline.

<sup>b</sup>Patients with multiple occurrences of the same event are counted under the highest severity

<sup>c</sup>Does not include death related to COVID-19, as they are captured as study outcome

<sup>d</sup>Per protocol, there was no provision for discontinuing participant evaluation and follow-up due to AEs. Therefore, all discontinuations due to AEs reflect death due to AEs.

<sup>e</sup>One participant (confirmed to be a resident, Subject ID (b) (6)) did not have their role (resident versus staff) identified in the dataset. In total, there were 5 deaths due to AEs in high-risk participants on bamlanivimab, although none were considered related to bamlanivimab administration.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Table 8.27.

**Table 14: Summary of Adverse Events, High Risk Participants in Prevention Population, Trial PYAD**

	Placebo (N = 282) n (%)	Bamlanivimab (N = 292) n (%)
TEAEs <sup>a</sup>	56 (20%)	60 (21%)
TEAEs by severity <sup>a,b</sup>		
Mild	28 (10%)	31 (11%)
Moderate	16 (6%)	16 (6%)
Severe	11 (4%)	11 (4%)
Missing	1 (<1%)	2 (1%)
Deaths due to AEs <sup>c,d</sup>	2 (1%)	5 (2%)
SAEs	12 (4%)	16 (6%)
Discontinuations from study participation due to AEs, including death <sup>d</sup>	2 (1%)	5 (2%)

Abbreviations: AE = adverse event, Bamlanivimab = 4200 mg bamlanivimab; COVID-19 = coronavirus disease 2019; n = number of participants in the selected category; N – number of participants in the Safety Population; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

<sup>a</sup>A TEAE is defined as an event that first occurred or worsened in severity after baseline.

<sup>b</sup>Patients with multiple occurrences of the same event are counted under the highest severity

<sup>c</sup>Does not include death related to COVID-19, as they are captured as study outcome

<sup>d</sup>Per protocol, there was no provision for discontinuing participant evaluation and follow-up due to AEs. Therefore, all discontinuations due to AEs reflect death due to AEs.

<sup>e</sup>One participant (confirmed to be a resident, Subject ID (b) (6)) did not have their role (resident versus staff) identified in the dataset. In total, there were 5 deaths due to AEs in high-risk participants on bamlanivimab, although none were considered related to bamlanivimab administration.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Table 8.28

**Table 15: Summary of Adverse Events, Immunocompromised Participants in Prevention Population, Trial PYAD**

	Placebo (N = 110) n (%)	Bamlanivimab (N = 115) n (%)
TEAEs <sup>a</sup>	27 (25%)	24 (21%)
TEAEs by severity <sup>a,b</sup>		
Mild	11 (10%)	8 (7%)
Moderate	8 (7%)	6 (5%)
Severe	7 (6%)	10 (9%)
Missing	1 (1%)	0 (<1%)
Deaths due to AEs <sup>c,d</sup>	3 (3%)	4 (4%)
SAEs	8 (7%)	12 (10%)
Discontinuations from study participation due to AEs, including death <sup>d</sup>	3 (3%)	4 (4%)

Abbreviations: AE = adverse event, Bamlanivimab = 4200 mg bamlanivimab; COVID-19 = coronavirus disease 2019; n = number of participants in the selected category; N – number of participants in the Safety Population; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

<sup>a</sup>A TEAE is defined as an event that first occurred or worsened in severity after baseline.

<sup>b</sup>Patients with multiple occurrences of the same event are counted under the highest severity

<sup>c</sup>Does not include death related to COVID-19, as they are captured as study outcome

<sup>d</sup>Per protocol, there was no provision for discontinuing participant evaluation and follow-up due to AEs. Therefore, all discontinuations due to AEs reflect death due to AEs.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Table 8.29

Common adverse events reported for the Safety Population in Trial PYAD (occurring in ≥1% in either the bamlanivimab or placebo arm)

included the preferred terms (PTs) urinary tract infection, fall, dizziness, arthralgia, and hypertension. Rates in the Safety Population were generally similar in bamlanivimab and placebo arms. No specific AE occurred at a rate of greater than 1% and more commonly than placebo in the Prevention Population. When considering only residents, confusional state and vulvovaginitis pruritus were both reported at a rate of 1% in the bamlanivimab arm compared to none in the placebo.

### Deaths

As of the January 13, 2021 database lock, 16 deaths occurred in Trial PYAD. Eleven deaths occurred in the Prevention Population, 4 deaths occurred in the Treatment Population, and 1 death occurred in a participant who had a SARS-CoV-2 positive antibody test at baseline.

Of the 16 total deaths, 5 were attributed to COVID-19 (4 deaths in the Prevention Population and 1 in the Treatment Population). All COVID-19 related deaths occurred in the placebo arm; none of the COVID-19 related deaths occurred in participants that received bamlanivimab. Eleven deaths were therefore considered to be adverse events, 7 of which occurred in the Prevention Population.

All 7 deaths in the Prevention Population occurred in residents who all met the definition of high risk. While there were more deaths in those who received bamlanivimab (n = 5) compared to placebo (n = 2), the individuals who died after bamlanivimab administration were on average older than those who died after placebo treatment (78 and 66 years old, respectively). None of the deaths due to adverse events were considered related to bamlanivimab administration. The average time to death for bamlanivimab treated participants in the Prevention Population was 66 days; the average time to death was also 66 days in the those treated with placebo. A summary of deaths due to adverse events is included in Table 16.

**Table 16: Summary of Deaths due to Adverse Events, Safety Population, Trial PYAD**

	Placebo N = 587 n (%)	Bamlanivimab N = 588 n (%)
<b>All Deaths Due to Adverse Event<sup>a</sup></b>	<b>6 (1%)</b>	<b>5 (1%)</b>
<b>Deaths by Population</b>		
<b>Prevention</b>	<b>2 (&lt;1%)</b>	<b>5 (1%)</b>
Acquired Immunodeficiency Syndrome	0 (0%)	1 (<1%)
Cardio-respiratory arrest	1 (<1%)	1 (<1%)
COPD	1 (<1%)	0 (0%)
Myocardial infarction	0 (0%)	1 (<1%)

Pneumonia	0 (0%)	1 (<1%)
Vascular dementia	0 (0%)	1 (<1%)
<b>Treatment</b>		
Cardiac Failure congestive	1 (<1%)	0 (0%)
COPD	1 (<1%)	0 (0%)
Dementia	1 (<1%)	0 (0%)
<b>Antibody Positive</b>		
Hypovolemic shock <sup>b</sup>	1 (<1%)	0 (0%)

Abbreviations: AE = adverse event; Bamlanivimab = 4200 mg bamlanivimab; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; IWRS = Interactive Web Response System; N = number of patients in the Safety Population; n = number of patients in specified category; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

<sup>a</sup>COVID-19-related deaths are not represented in this table. Deaths attributed to COVID-19 are part of the efficacy endpoint analysis and were not captured as AEs per protocol. Four COVID-19-related deaths occurred in the placebo study arm in the Prevention Population, and 1 COVID-19-related death occurred in the placebo study arm in the Treatment Population. No COVID-19-related deaths occurred in the bamlanivimab study arm.

<sup>b</sup>One patient who was enrolled to receive placebo, tested positive for SARS-CoV-2 by baseline antibody test. This participant still received blinded study drug (placebo) and died on post-infusion Day 69 of hypovolemic shock.

Source: Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Table 8.34

### Serious Adverse Events

Serious adverse events occurred at comparable rates in the Safety and Prevention Populations. In both the Safety and Prevention Population, as well as participants considered to be high risk, urinary tract infection and atrial fibrillation occurred more commonly in those that received bamlanivimab 4,200 mg compared to placebo, but these events were rare and occurred at a rate of 1% or less. In residents and immunocompromised participants, only urinary tract infection occurred in at least 2 bamlanivimab treated participants and more commonly than placebo (Table 17).

**Table 17: Preferred Terms Occurring in ≥2 Participants in Bamlanivimab Arm and Greater Than Placebo arm for Safety Population, Prevention Population, Residents, High Risk, and Immunocompromised Participants, Trial PYAD**

	Placebo	Bamlanivimab
<b>Safety Population</b>	<b>N = 587</b>	<b>N = 588</b>
Participants with ≥1 SAE (n, %)	19 (3%)	22 (4%)
Urinary tract infection (n, %)	0 (0%)	4 (1%)
Atrial fibrillation (n, %)	0 (0%)	2 (<1%)
<b>Prevention Population</b>	<b>N = 482</b>	<b>N = 484</b>
Participants with ≥1 SAE (n, %)	<b>13 (3%)</b>	<b>19 (4%)</b>
Urinary Tract Infection	0 (0%)	3 (1%)
Atrial fibrillation	0 (0%)	2 (<1%)
<b>Residents</b>	<b>N = 139</b>	<b>N = 160</b>
Participants with ≥1 SAE (n, %)	10 (7%)	14 (9%)
Urinary tract infection (n, %)	0 (0%)	2 (1%)
<b>High Risk</b>	<b>N = 282</b>	<b>N = 292</b>
Participants with ≥1 SAE (n, %)	12 (4%)	16 (6%)



Urinary tract infection (n, %)	0 (0%)	2 (1%)
Atrial fibrillation (n, %)	0 (0%)	2 (1%)
<b>Immunocompromised</b>	<b>N = 110</b>	<b>N = 115</b>
Participants with ≥1 SAE (n, %)	8 (7%)	12 (10%)
Urinary tract infection (n, %)	0 (0%)	2 (2%)

Source: Created by FDA Reviewer using data from Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request, Table 8.35 and Regulatory Response dated May 17, 2021, Table 5.1  
Abbreviations: SAE = serious adverse event; Bamlanivimab = 4200 mg bamlanivimab

### *Laboratory Findings*

Laboratory samples for hematology and clinical chemistry assessments were drawn on Days 1, 29, 57, at the end of treatment visit, and at follow-up on Days 85 and 141. No clinically meaningful difference in any specific laboratory parameters were observed between the bamlanivimab and placebo arms.

### Analysis of Submission-Specific Safety Issues

#### *Hypersensitivity and Infusion-Related Reactions*

To identify potential hypersensitivity reactions, an analysis using narrow and broad terms within three Standard Medical Dictionary for Regulatory Activities queries, Anaphylactic Reaction, Angioedema, and Hypersensitivity was completed by Eli Lilly. Events occurring within the first 24 hours following infusion are considered immediate hypersensitivity reactions and are shown in Table 19. Overall, events of immediate hypersensitivity were rare. Of note, no immediate hypersensitivity reactions were reported from residents or immunocompromised participants who received bamlanivimab within the Prevention Population. There were no events of anaphylaxis during Trial PYAD.

Of the identified infusion-related reactions in the Safety Population of Trial PYAD, one was determined to be an SAE. An 18-year-old male participant with a history of migraines received bamlanivimab 4200 mg in the Treatment Population. The reaction began 10 minutes into the infusion with bamlanivimab and the infusion was stopped. The participant initially reported runny nose, but then developed swelling of the right eye and throat. The patient was treated with IV diphenhydramine and then transferred to the emergency room where he received additional IV diphenhydramine and steroids. The patient was discharged from the emergency room and was reported as recovered the following day.

**Table 18: Immediate Hypersensitivity Events for Safety Population, Prevention Population, and High Risk Participants, Trial PYAD**

	Bamlanivimab 4200 mg
<b>Safety Population</b>	<b>N = 588</b>
Urticaria	2 (<1%)
Erythema	1 (<1%)
Hypersensitivity	1 (<1%)

Rash	1 (<1%)
<b>Prevention Population</b>	<b>N = 484</b>
Urticaria	2 (<1%)
Erythema	1 (<1%)
Hypersensitivity	1 (<1%)
Rash	1 (<1%)
<b>High Risk</b>	<b>N = 292</b>
Urticaria	1 (<1%)
Rash	1 (<1%)

Source: Created by FDA Reviewer using data from Amendment to Emergency Use Authorization for Bamlanivimab (EUA 90) Request and Regulatory Response dated May 17, 2021, Table 5.1

Non-immediate (occurring greater than 24 hours after end of study drug administration) hypersensitivity reactions were also identified using the same analysis (Table 19). Events were rare overall. The event of cardiorespiratory arrest occurred 58 days after bamlanivimab infusion and was not considered to be related to bamlanivimab administration. No non-immediate hypersensitivity reactions were reported from immunocompromised participants who received bamlanivimab within the Prevention Population.

**Table 19: Hypersensitivity Events After the First 24 Hours for Safety Population, Prevention Population, Residents, and High Risk Participants, Trial PYAD**

	Bamlanivimab 4200 mg
<b>Safety Population</b>	<b>N = 588</b>
Rash	2 (<1%)
Swelling face	1 (<1%)
Urticaria	1 (<1%)
Cardio-respiratory arrest	1 (<1%)
Dyspnea	1 (<1%)
Edema	1 (<1%)
Erythema	1 (<1%)
Mouth ulceration	1 (<1%)
Pruritus	1 (<1%)
<b>Prevention Population</b>	<b>N = 484</b>
Rash	1 (<1%)
Urticaria	1 (<1%)
Swelling Face	1 (<1%)
Pruritus	1 (<1%)
Dyspnea	1 (<1%)
Erythema	1 (<1%)
Edema	1 (<1%)
Cardio-respiratory arrest	1 (<1%)
<b>Residents</b>	<b>N = 160</b>
Cardio-respiratory arrest	1 (1%)
<b>High Risk</b>	<b>N = 292</b>
Urticaria	1 (<1%)
Rash	1 (<1%)
Cardio-respiratory arrest	1 (<1%)
Dyspnea	1 (<1%)
Pruritus	1 (<1%)

### *Antiviral Resistance*

Bamlanivimab 700 mg was originally authorized on November 9, 2020, for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. This authorization was ultimately revoked on April 16, 2021 in the context of the increased frequency of SARS-CoV-2 variants circulating in the United States that were resistant to bamlanivimab alone.

Bamlanivimab 700 mg and etesevimab 1,400 mg administered together are currently authorized for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in certain patients who are at high risk for progression to severe COVID-19, including hospitalization and death. Evaluation of susceptibility of SARS-CoV-2 viral variants identified through global surveillance to bamlanivimab and etesevimab is ongoing.

Since the initial authorization of bamlanivimab and etesevimab administered together for emergency use, several SARS-CoV-2 viral variants that are resistant to bamlanivimab and etesevimab have been circulating throughout the United States. Based on neutralization data generated from authentic virus assays and/or pseudotyped virus-like particle (VLP) assays, it is likely that bamlanivimab and etesevimab together retain activity against the B.1.1.7 (Alpha; UK origin) and B.1.617.2/AY.3 variants (Delta; India origin), but do not retain activity against B.1.351 (Beta; South Africa origin), P.1 (Gamma; Brazil origin), AY.1/AY.2 ("Delta plus"; India origin), or B.1.621 (Mu; Colombia origin) variants. In authentic virus assays, bamlanivimab and etesevimab together had reduced activity (11-fold) against B.1.427/B.1.429 (Epsilon; USA [California] origin) and B.1.526 (Iota; USA [New York] origin); reductions in activity were also seen in pseudotyped VLP assays for these variants of 9- and 30-fold, respectively, and for the B.1.617.1 (Kappa; India origin) variant of 6-fold.

It is unclear how small reductions in susceptibility to bamlanivimab and etesevimab seen in authentic or recombinant SARS-CoV-2 or pseudotyped VLP assays correlate with clinical outcomes. Available nonclinical and clinical PK data indicate that etesevimab at the authorized dose may retain activity against the B.1.526 variant clinically, although only very limited data are currently available from patients infected with this variant in clinical trials. Preliminary clinical evidence indicates that the administration of bamlanivimab and etesevimab together results in similar viral shedding reductions in participants infected with the L452R variant (Epsilon; California origin) as for those infected with bamlanivimab-sensitive strains. Of the 134 participants infected with the L452R

variant at baseline in the Phase 3 portion of BLAZE-1, 3 of the 50 individuals treated with placebo (6%) and 1 of the 84 participants treated with bamlanivimab 700 mg and etesevimab 1,400 mg (1%) were hospitalized, although this did not reach statistical significance ( $p=0.15$ ), possibly due to small sample size.

Because bamlanivimab and etesevimab are not thought to be active against B.1.351 (Beta), P.1 (Gamma), AY.1/AY.2 (“Delta plus”), and B.1.621 (Mu) variants, the prevalence of these variants is closely monitored. Authorized labeling for bamlanivimab and etesevimab administered together advises healthcare providers to initiate treatment as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of onset of symptoms. Testing technologies are not available for healthcare providers to obtain information prior to initiating treatment to ascertain whether a patient who has tested positive for SARS-CoV-2 is infected with a particular viral variant that is resistant to bamlanivimab and etesevimab. As such, there is a significant risk of treatment failure should bamlanivimab and etesevimab be administered to a patient who is infected with a resistant SARS-CoV-2 variant. Previously, shipping of bamlanivimab and etesevimab had been paused in states with higher prevalence of resistant variants.

On August 27th, 2021, a Limitations of Authorized Use for bamlanivimab and etesevimab, administered together, was added to only authorize use in states, territories, and U.S. jurisdictions where combined frequency of variants resistant to bamlanivimab and etesevimab, administered together, is less than or equal to 5%.

In order to minimize the burden to health care providers, FDA has provided a listing of states, territories, and U.S. jurisdictions in which bamlanivimab and etesevimab are authorized (<https://www.fda.gov/media/151719/download>). In collaboration with the Assistant Secretary for Preparedness and Response (ASPR) and CDC, it has been determined that bamlanivimab and etesevimab will be authorized when under the following conditions:

1. An HHS Region has a combined proportion of variants resistant to bamlanivimab and etesevimab that is less than or equal to 5% over a 4-week period.
2. No state within the HHS Region has a combined proportion of variants resistant to bamlanivimab and etesevimab greater than 5%.
3. The two most recent weeks of data from Nowcast predicts the combined prevalence of variants resistant to bamlanivimab and etesevimab will remain below 5%.

Since June 2021, there has been a sustained increase in the circulation of the B.1.617.2/Delta variant; it is now the dominant variant in the United States. The increase in prevalence of B.1.617.2 has been associated with a concomitant decrease in the frequency of identified variants that are expected to be resistant to bamlanivimab and etesevimab. As such, bamlanivimab and etesevimab are

now authorized for use for treatment in all 50 states, as well as in territories and U.S. jurisdictions, based on currently available data. It is therefore reasonable to authorize bamlanivimab and etesevimab for post-exposure prophylaxis in these locations as well.

The assessment of resistance variants across the development program is ongoing. Based on the Phase 3 portion of BLAZE-1, treatment-emergent variants were observed in 9.0% (42/467) of patients treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together, in 5.3% (21/394) of patients treated with bamlanivimab 700 mg and etesevimab 1,400 mg together, and in 4.0% (27/674) of patients treated with placebo. It is possible that treatment-emergent resistance to both bamlanivimab and etesevimab is more likely to occur in subjects infected with variants which have reduced susceptibility to one of the mAbs, for example, B.1.617.2 (Delta), to which bamlanivimab alone has reduced activity (>1,136-fold) in an authentic virus assay. However, the frequency of such occurrences and impact on clinical outcomes is not known at present.

It is recommended that patients infected with COVID-19 and treated with bamlanivimab and etesevimab 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 in order to limit viral transmission to others and reduce this theoretical risk.

#### *Antibody-Vaccine Interaction*

It is unclear how treatment with bamlanivimab and etesevimab together for post-exposure prophylaxis in an unvaccinated individual will affect the response to vaccination in the future. The Division of Antiviral sought advice related to this issue from the Center for Biologics Evaluation and Research, National Institutes of Health (NIH), and CDC. Studies to address a potential interaction are ongoing.

#### *Anti-Drug Antibodies*

Samples for the immunogenicity assessment have been collected and are stored. The Applicant submitted data to support validation of anti-drug antibody (ADA) assays (screening, confirmatory, and titer assays), which remains under review at the time of authorization. Stored patient samples are scheduled to begin sample analysis. The ADA incidence and the effect of ADA after a single dose of bamlanivimab and etesevimab on PK, efficacy and safety are currently unknown.

Monoclonal antibodies are considered to have low immunogenicity risk and the target is the spike protein of SARS-CoV-2, which is an exogenous target. In

addition, for the EUA, bamlanivimab and etesevimab will be administered together as a single dose treatment.

#### *Antibody-Dependent Enhancement of Infection*

To date, there are no compelling data to support the occurrence of antibody-dependent enhancement (ADE) of infection following administration of bamlanivimab and etesevimab when administered together (please see Section XIII, Nonclinical Data to Support Efficacy for more information related to ADE). In addition, ADE would likely not be a concern in the context of bamlanivimab and etesevimab being given for post-exposure prophylaxis.

## **X. Specific Populations**

### Rationale for Inclusion of Pediatric Patients Under EUA

As of September 2, 2021 over 5 million children have tested positive for COVID-19 in the United States, Puerto Rico, and Guam (<https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/>). Based on these data, children represent 26.8% of all COVID-19 cases. While COVID-19 is typically milder in children, some pediatric patients require hospitalization and ICU-level care (Götzinger et al. 2020). Given that COVID-19 can be a serious and life-threatening disease in adolescent patients (particularly in those with risk factors for the development of severe illness and hospitalization), the similarities in physiology to adults, the similar PK in adolescents weighing  $\geq 40$  kg based on modeling, and the safety profile, and the lack of authorized vaccines for adolescents under the age of 16, there is prospect of benefit for this patient population. Based on the totality of evidence to support the prospect of benefit, and that it is reasonable to believe the known and potential benefits outweigh the known and potential risks, the authorization of bamlanivimab and etesevimab administered together for post-exposure prophylaxis also includes adolescents who are 12 years of age and older and who weigh at least 40 kg.

### Dose Considerations for Specific Populations

- Safety and pharmacokinetic (PK) data are not available in children younger than 12, pregnant women, lactating women, patients with renal insufficiency, or patients with moderate or severe hepatic insufficiency. No dosage adjustment is recommended based on age (12 to 86 years of age), sex, race, body weight (40 to 173 kg), renal or mild hepatic impairment, during pregnancy or while lactating, or for disease severity.
- Nonclinical reproductive toxicology studies with bamlanivimab and etesevimab have not been conducted.

- No binding of clinical concern was observed in tissue-cross reactivity studies in select human fetal tissues with either bamlanivimab or etesevimab.
- No specific risks to pregnant or lactating women have been identified based on the nonclinical safety data.

## **XI. Clinical Pharmacology**

### Pharmacokinetics

- Pharmacokinetic (PK) profiles of bamlanivimab and etesevimab were assessed in a previous submission of this EUA.
- There are no changes to the PK assessment in the present submission.

### Rationale for Dose

#### *Addition of Post-Exposure Prophylaxis Indication*

- In Study PYAD (BLAZE-2), bamlanivimab 4,200 mg reduced incidence of mild or worse severity COVID-19 by 40% relative to placebo in residents and staff of skilled nursing and assisted living facilities following identification of an index case within a facility. (See Section VIII for more details)
- Combination therapy, i.e., bamlanivimab and etesevimab, is preferred over monotherapy, i.e., bamlanivimab alone. EUA 90 for bamlanivimab alone was revoked due to reduced susceptibility to emerging variants. Combination therapy reduces the impact of resistance emergence.
- Post-exposure prophylaxis is comparable to early treatment if adequate antiviral activity is maintained during the treatment period of 14 days. The majority of patients with COVID-19 in Study PYAB cleared virus within 14 days as indicated by a cycle threshold  $\geq 37$  even without treatment, although viral shedding decreased more quickly in treated patients. Thus, antiviral activity from a therapeutic agent is only expected to have clinical benefit during the first 14 days.
- In a treatment study (PYAB; BLAZE-1), bamlanivimab 700 mg and etesevimab 1,400 mg administered together to patients with COVID-19 decreased the rate of hospitalizations and mortality relative to placebo and resulted in concentrations above each antibody's respective in vivo concentration expected to achieve 90% of antiviral effect (EC90) over 28 days, indicating near-maximal antiviral activity.
- Therefore, a dosage of bamlanivimab 700 mg and etesevimab 1,400 mg administered together is expected to provide comparable efficacy to bamlanivimab 4,200 mg for post-exposure prophylaxis.

#### *For SARS-CoV-2 Variants*

- To assess the effect of bamlanivimab and etesevimab administered together against variants of concern, antiviral activity for up to 4 weeks

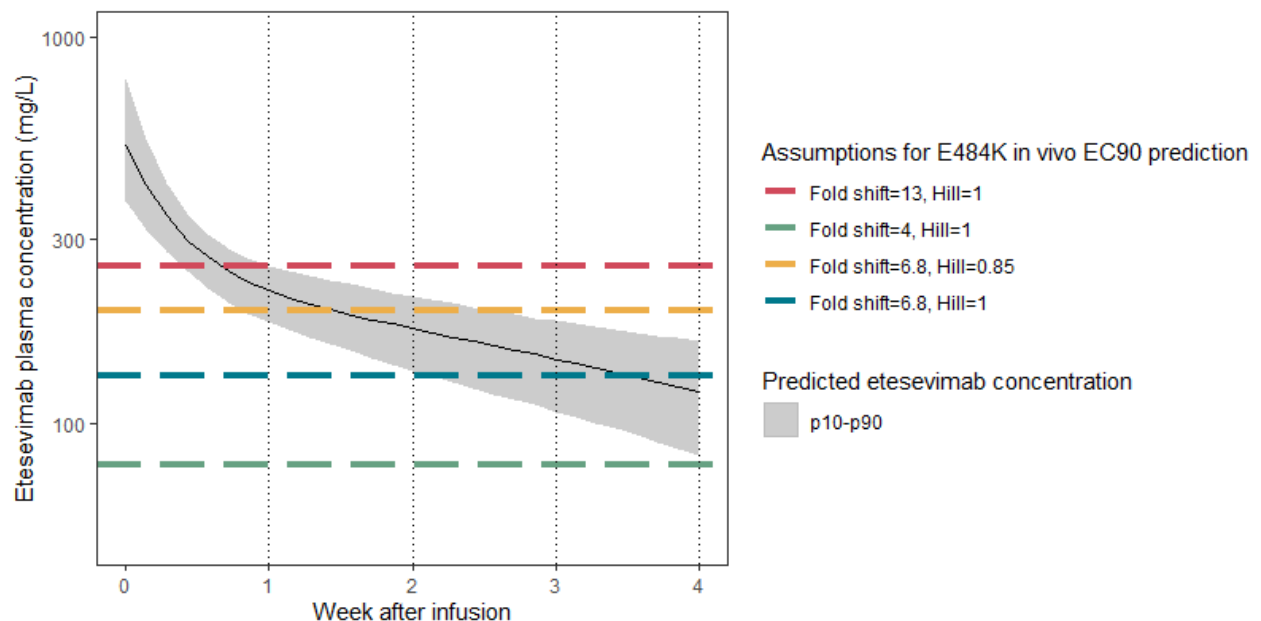
against each variant was assessed using the ratio of bamlanivimab and etesevimab concentration at 2 and 4 weeks after administration of the proposed dose to in vivo EC90 value. A duration of 2 weeks was assessed because antiviral activity is only expected to have clinical benefit during this time period. Additionally, a duration of 4 weeks was assessed to maintain consistency with the initial EUA for bamlanivimab and etesevimab where 4 weeks was considered necessary for clinical effectiveness and to include a more conservative duration estimate.

- **Wild-type virus:** The median ratio (10<sup>th</sup> percentile, 90<sup>th</sup> percentile) of concentration after administration of the proposed dose to in vivo EC90 value estimated from the PK-PD modeling was 6.9 (5.3-8.6) and 3.8 (2.6-5.4) at Weeks 2 and 4 for bamlanivimab and 9 (6.9-11.1) and 6.3 (4.1-8.6) at Weeks 2 and 4 for etesevimab, indicating near-maximal antiviral activity over at least 4 weeks.
- **B.1.1.7 (UK origin) and B.1.427/429 (California origin) variants:** The proposed dose of bamlanivimab and etesevimab administered together is expected to retain antiviral activity against variants from B.1.1.7 and B.1.427/429 lineages. For both variants, at least one antibody retains near-maximal antiviral activity for 4 weeks as determined using the ratio of plasma concentration to expected in vivo EC90 value for variants of concern. The in vivo EC90 value was determined using the in vivo EC90 value for wild-type virus corrected for decreased susceptibility identified in a pseudotyped VLP assay. Concentrations of bamlanivimab and etesevimab at 4 weeks are higher than the variant-specific in vivo EC90 value and are expected to retain antiviral activity despite changes in antiviral susceptibility for each variant. Activity against the B.1.427/429 variant is also supported by clinical data (See Section IX for more details).
- **B.1.526 (New York origin) variant:** The proposed dose of bamlanivimab and etesevimab administered together is expected to retain antiviral activity against variants with the E484K substitution, including those of the B.1.526 lineage, for up to 14 days using a totality of evidence approach. Using in vivo EC90 values corrected for the change in susceptibility from a pseudotyped VLP assay, etesevimab is expected to provide adequate antiviral coverage for 2 weeks when assessed using the expected value (fold shift of 6.8 relative to wild-type strain) but not at higher limits of expected in vivo EC90 value as shown in Figure 2, and bamlanivimab showed no antiviral activity. In a recombinant authentic virus assay, etesevimab showed minimal change in susceptibility when comparing the wild-type virus with virus harboring the E484K substitution. Recombinant authentic virus assays may be more relevant to the clinical setting than pseudotyped VLP assays, although correlations with clinical efficacy have yet to be determined. However, the pseudotyped VLP data may be more robust because it has been repeated several times. Virologic data are available for 7 patients in whom the E484K substitution was detected



at baseline (2 placebo, 5 bamlanivimab and etesevimab administered together); while there may have been a trend towards antiviral activity in subjects treated with bamlanivimab and etesevimab compared with placebo, there were too few subjects to draw firm conclusions. Each approach that was taken to determine whether bamlanivimab and etesevimab may be effective against variants with the E484K substitution has its limitations, but together they indicate that etesevimab likely retains antiviral activity against variants harboring the E484K substitution, including those of the B.1.526 lineage, for post-exposure prophylaxis and treatment.

**Figure 2. Etesevimab Concentration-Time Profile After Administration of Proposed Dose and Potential In Vivo EC90 Values for the B.1.526 (New York Origin) Variant.**



This figure shows the sensitivity of the in vivo EC90 value calculated from PK-PD modeling for the wild-type variant corrected for the change in susceptibility identified from the pseudotyped virus-like particle assay. The dashed lines represent multiple estimates of in vivo EC90 value. The turquoise dashed line (EC50 fold change=6.8 and Hill coefficient=1) represents the expected value of the in vivo EC90 using the mean value from the pseudotyped virus-like particle assay. The other dashed lines represent the in vivo EC90 value under various assumptions of fold change in susceptibility relative to the wild-type strain and Hill coefficient in a sensitivity analysis, including conservative assumptions of the upper bound of 95% CI of fold change or a lower Hill coefficient, which emphasizes that the in vivo EC90 value is sensitive to underlying assumptions observed in the pseudotyped virus-like particle assay.

- **B.1.351 (South Africa origin) and P.1 (Brazil origin) variants:** The proposed dose of bamlanivimab and etesevimab administered together is not expected to retain antiviral activity against variants of the B.1.351 and P.1 lineages due to insufficient inhibition in a pseudotyped VLP assay.

- The in vivo EC90 values generated from PK-PD modeling are comparable to the in vitro EC90 values with the Applicant's proposed 6.5% lung penetration based on their PBPK model. Limitations to relying on the expected 6.5% lung penetration include 1) lack of clinical observations of bamlanivimab and etesevimab lung concentrations in patients, 2) uncertainty regarding relevant respiratory tract site of action (e.g., epithelial lining fluid or interstitial space), and 3) significant interpatient variability in the available epithelial lining fluid data supported by bronchoalveolar lavage for other monoclonal antibodies.

Rationale for dosing recommendations in pediatric patients and other specific populations:

- PK of bamlanivimab and etesevimab in specific populations was assessed in a previous submission of this EUA.
- There are no changes to the assessment of specific populations in the present submission.

## **XII. Nonclinical Data to Support Safety**

- For Bamlanivimab
  - A 3-week nonclinical toxicology study with bamlanivimab was conducted in Sprague Dawley rats.
    - No findings of significant clinical concern were noted at systemic exposures greater than 40 times the exposure in humans at the authorized human dose.
    - Non adverse findings of unclear clinical relevance included:
    - An increase in neutrophils.
    - Liver findings including lipidosis, increased liver weight, and pale coloring.
    - Findings in lymph nodes including increased cellularity.
  - GLP tissue cross-reactivity studies were conducted with bamlanivimab using normal adult human, monkey, and rat tissues. No binding of clinical concern was observed.
  - Single dose PK studies with bamlanivimab were conducted in Sprague Dawley rats and cynomolgus monkeys. Clearance of bamlanivimab was similar between both species (23 to 25 ml/hr/kg); and the volume of distribution was 105 and 83.5 ml/kg in rats and monkeys, respectively.
- For Etesevimab
  - Etesevimab was evaluated in a GLP 3-week repeat-dose toxicology study in cynomolgus monkeys with a 6-week recovery using intravenous dosing.
    - No adverse, drug-related findings were observed up to the highest dose tested (410 mg/kg/week). The safety factor at the

NOAEL of 410 mg/kg is approximately 18 at the authorized human dose.

- GLP tissue cross-reactivity studies were also conducted in normal adult human and cynomolgus monkey tissues. No binding of clinical concern was observed with etesevimab in either species in these studies.

### **XIII. Nonclinical Data to Support Efficacy**

Please refer to the original EUA 94 authorization review dated February 9, 2021 for an overview of the non-clinical data to support efficacy. Updated information for directed evolution and cell culture passage experiments, and evaluation of amino acid substitutions in pseudotyped virus-like particle (VLP) and recombinant virus assays is presented below. A prophylaxis study with bamlanivimab and etesevimab administered together in African green monkeys is also summarized.

- Resistant variants were identified using directed evolution of the spike protein and serial passage in cell culture of SARS-CoV-2 in the presence of bamlanivimab or etesevimab individually. Resistant variants were not identified when bamlanivimab and etesevimab were tested together using the same methodology. Viral variants identified in these studies that had reduced susceptibility to bamlanivimab included spike protein amino acid substitutions E484D/K/Q, F490S, Q493R, and S494P, and variants that had reduced susceptibility to etesevimab included substitutions K417N, D420N, and N460K/S/T/Y. Neutralization assays using SARS-CoV-2 and vesicular stomatitis virus (VSV) virus-like particles (VLP) pseudotyped with variant SARS-CoV-2 spike protein confirmed reductions in susceptibility to the selecting antibody. Retention of susceptibility to the other antibody alone was observed, with the exception of the E484D and Q493R substitution. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of those with E484D, E484K, E484Q, and Q493R substitutions, which had reduced susceptibility of 145-fold, 24-fold, 17-fold, and [REDACTED] respectively in a pseudotyped VLP assay.
- Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing. Pseudotyped VLP evaluation of amino acid substitutions identified in global surveillance showed that the V483A substitution reduced susceptibility to bamlanivimab 48-fold, but activity was maintained with etesevimab, and with bamlanivimab and etesevimab together. N501Y and N501T substitutions reduced susceptibility to etesevimab approximately 5-fold and 20-fold, respectively. Activity against variants with N501Y or N501T substitutions was maintained with bamlanivimab alone, and with bamlanivimab and etesevimab together.
- Bamlanivimab and etesevimab together retained activity against a SARS-CoV-2 B.1.1.7 lineage (Alpha; UK origin) virus and related pseudotyped VLPs expressing the spike protein found in the B.1.1.7 variant. SARS-CoV-2

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B.1.351 lineage (Beta; South Africa origin) virus and related pseudotyped VLPs expressing spike proteins from B.1.351 lineage or substitutions K417N + E484K + N501Y found in this lineage had reduced susceptibility to bamlanivimab and etesevimab together of >324, 431-fold or >45-fold, respectively. Pseudotyped VLPs expressing spike protein from the P.1 lineage (Gamma; Brazil origin) or K417T + E484K + N501Y found in the P.1 lineage had reduced susceptibility to bamlanivimab and etesevimab together of 252-fold or [REDACTED], respectively.

- Bamlanivimab and etesevimab together and etesevimab alone retained activity against SARS-CoV-2 B.1.617.2 lineage (Delta; India origin) virus and related pseudotyped VLPs, but bamlanivimab alone had reduced activity (>1,136 and >1,868-fold, respectively). Bamlanivimab and etesevimab are expected to retain activity against B.1.617.2 sublineage AY.3 (India origin). B.1.617.2 sublineages AY.1/AY.2 (commonly known as “Delta plus”; India origin) have an additional K417N substitution; pseudotyped VLPs expressing AY.1/AY.2 related spike sequence had a reduced susceptibility to bamlanivimab and etesevimab together of 1,235-fold. SARS-CoV-2 recombinant virus containing the L452R substitution present in B.1.427/B.1.429 lineages (Epsilon; USA [California] origin) and pseudotyped VLPs expressing the full-length spike protein or the L452R substitution found in this lineage showed reduced susceptibility to bamlanivimab and etesevimab together of 11-fold, 9-fold, or 5-fold, respectively. Pseudotyped VLPs expressing spike protein from the B.1.617.1 lineage (Kappa; India origin) showed reduced susceptibility to bamlanivimab and etesevimab together of 6-fold; for this variant, susceptibility to etesevimab alone was maintained, but not to bamlanivimab alone (>1,030-fold reduction). Bamlanivimab and etesevimab together and etesevimab alone retained activity against pseudotyped VLPs expressing the full-length spike protein from the C.37 lineage (Lambda; Peru origin), but bamlanivimab alone had reduced activity (>2,112-fold reduction). Pseudotyped VLPs expressing spike protein from the B.1.621 lineage (Mu; Colombia origin) show reduced susceptibility to bamlanivimab and etesevimab together of 116-fold, due to susceptibility reductions to bamlanivimab (>1,863-fold) and etesevimab (17-fold) alone.
- In authentic SARS-CoV-2 assays, bamlanivimab and etesevimab together retained activity against variants of B.1.1.7 (Alpha) and B.1.617.2/AY.3 (Delta) lineages, although bamlanivimab alone had reduced activity to B.1.617.2/AY.3 (Delta) in this assay (>1,136-fold). Bamlanivimab and etesevimab had reduced activity (>325-fold) against the B.1.351 (Beta) variant in an authentic virus assay.
- SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the E484K substitution present in the B.1.526 lineage (Iota; USA [New York] origin) or the L452R substitution present in the B.1.427/B.1.429 lineage (Epsilon; USA [California] origin) showed reduced susceptibility to bamlanivimab and etesevimab together of 11-fold. Susceptibility to etesevimab alone was

maintained for both isolates, but not to bamlanivimab alone (>833-fold and >1,460-fold reduction for E484K and L452R viruses, respectively).

- A study using the African green monkey model of SARS-CoV-2 infection was conducted to evaluate the risk of antibody-dependent enhancement (ADE) of infection, using neutralizing and sub-neutralizing concentrations of bamlanivimab and etesevimab administered together. Animals (n=6 per group) were administered intravenous doses of bamlanivimab and etesevimab at 0.05, 0.5, or 20 mg/kg of each antibody, or isotype controls at 20 mg/kg, one day prior to intranasal and intratracheal inoculation with SARS-CoV-2 (USA WA1/2020 isolate). Overall, treatment with 0.5 mg/kg or 20 mg/kg doses resulted in a significant reduction in genomic and sub-genomic viral RNA in lung tissue; at the 20 mg/kg dose there was also a significant reduction in sub-genomic RNA in bronchioalveolar fluid. In general, there was no increased viral replication at any dose, indicating a lack of antibody-dependent enhancement of infection.

#### XIV. Supply Information

- Bamlanivimab is available in single use vials containing bamlanivimab 700 mg/20 mL per vial. Each dose requires one vial of bamlanivimab.
- Etesevimab is available in single use vials containing etesevimab 700 mg/20 mL per vial. Each dose requires two vials of etesevimab.

Table 20 below provides supply projections for bamlanivimab and etesevimab as of September 2021.

**Table 20: Summary of Supply Projections for Bamlanivimab and Etesevimab**

Supply projection	Bamlanivimab vials & doses	Etesevimab (doses)	Treatments
Sep 2021	(b) (4)		
Oct 2021			
Nov 2021			
Dec 2021			
Jan 2022			
Feb 2022			
<b>Total</b>			

The Applicant stated that the excess of etesevimab is intended to be used to pair with existing supply of bamlanivimab. As communicated on September 10, 2021, (b) (4)

## XV. Chemistry, Manufacturing, and Controls Information

- Bamlanivimab and etesevimab are recombinant neutralizing human immunoglobulin G-1 (IgG1 variant) monoclonal antibodies. Both antibodies are produced in a Chinese Hamster Ovary (CHO) cell line and were designed to target different but overlapping epitopes in the Receptor Binding Domain (RBD) of the spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By binding to the spike protein, the antibodies block the virus attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, preventing subsequent viral entry into human cells and viral replication resulting in decreased viral shedding and transmission. The following provides additional information on each antibody:
  - Bamlanivimab has a molecular weight of 146 kDa and consists of 2 identical light chain polypeptides composed of 214 amino acids each and 2 identical heavy chain polypeptides composed of 455 amino acids. Bamlanivimab also exhibits antibody-dependent cell mediated cytotoxicity (ADCC) activity.
  - Etesevimab has a molecular weight of 145 kDa and consists of 2 identical light chain polypeptides composed of 216 amino acids each and 2 identical heavy chain polypeptides composed of 449 amino acids. Etesevimab contains two leu-to-ala (LALA) substitutions, at the 234th and 235th positions of the heavy chain, to reduce antibody-dependent cell mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activity.
- Bamlanivimab and etesevimab are available as concentrated solutions in separate vials and must be diluted and combined prior to IV administration. Each antibody is available as follows:
  - Bamlanivimab Injection, 700 mg/20 mL vial, is a sterile solution formulated in (b) (4) at pH (b) (4), consisting of (b) (4) histidine (b) (4), 50 mM sodium chloride, 6.0% sucrose, 0.05% w/v polysorbate 80, and water for injection.
  - Etesevimab Injection, 700 mg/20 mL vial, is a sterile solution formulated in (b) (4) at pH (b) (4), consisting of (b) (4) histidine (b) (4), 8.04% sucrose, 0.05% w/v polysorbate 80, and water for injection.
- INDs 150440 for bamlanivimab, and 150707 for etesevimab, were referenced for this EUA and contains the supporting CMC information. The data submitted in INDs 150440 and 150707 support the conclusion that the manufacture of bamlanivimab and etesevimab is sufficiently controlled and

leads to a product that is suitable for use under EUA. A non-compendial sterility test is used to release the bamlanivimab and etesevimab drug product with (b) (4) sensitivity. For the purpose of EUA, this test is sufficient to allow for timely delivery to patients. A full method validation to demonstrate that this non-compendial method is equivalent to or better than the compendial method is expected should the Eli Lilly pursue licensure of bamlanivimab and etesevimab.

- Several major drug substance and drug product manufacturing changes were made during development of bamlanivimab and etesevimab, including changes in the cell lines, manufacturing scales, processes, and facilities. The analytical comparability data support that the material proposed for use under the EUA is comparable to the material used in the supporting clinical studies. Differences in charge heterogeneity, glycan profile, Fc receptor binding (bamlanivimab only), and ADCC activity (bamlanivimab only) identified between the material used in the early clinical studies and the EUA are not expected to change the benefit/risk analysis at the intended dose and patient population proposed for the EUA.
- The expiration dating periods for bamlanivimab and etesevimab were requested as follow:
  - For bamlanivimab, the requested expiration dating period of 18 months at 2°C to 8°C is supported by a risk assessment of the available drug product stability data including up to 9 months at the long-term storage condition of 2°C to 8°C and 9 months at the accelerated storage condition of 25°C/60% RH. Drug substance stability data for 1 month at the stress condition of 40°C further support expiry dating. In these studies, these stability data indicate that the product remains stable and within the stability specifications with minor expected trends. Eli Lilly committed to update, in a timely manner, IND 150440 with additional stability data from ongoing studies to further support the proposed 18-month dating period.
  - For etesevimab, the requested expiration dating period of 12 months at 2°C to 8°C is supported by a risk assessment of the available drug product stability data from DP4, the proposed EUA material, and DP2, which is comparable to DP4. The available stability data include up to 6 months at the long-term storage condition of 2°C to 8°C and 6 months at the accelerated storage condition of 25°C/60% RH. Drug substance stability data for 1 month at the stress condition of 35°C further support expiry dating.

In these studies, these stability data indicate that the product remains stable and within the stability specifications with minor expected trends. Eli Lilly committed to update, in a timely manner, IND 150707 with additional stability data from ongoing studies to further support the proposed 12-month dating period.

- Data supports the assessment that the viscosity of diluted bamlanivimab and etesevimab is similar to normal saline. Further, the data supports that flow rates during administration by gravity drip can be controlled and can reach the maximal flow rates recommended in the fact sheet.
- Eli Lilly plans to use additional manufacturing sites for etesevimab drug substance and drug product for this EUA. The data (e.g., comparability and manufacturing process control) supporting additional manufacturing sites will be submitted to IND 150707 prior to use. These data will be reviewed in a timely manner to allow rapid use of product from these sites in the EUA. Refer to the section below regarding inspections.

## XVI. Manufacturing Site Inspections

The following manufacturing and testing facilities are acceptable for bamlanivimab and etesevimab manufacture for the purpose of the EUA

**Table 21: Manufacturing and testing Sites for Bamlanivimab**

Manufacturing Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant	Inspection Dates	GMP Status (if known)
ImClone Systems LLC d.b.a Eli Lilly and Company (FEI 3002889358)	Drug substance manufacturing, in-process testing	Branchburg, NJ	IND 150440	Eli Lilly and Company	08/21/2020	Official Action Indicated <sup>1</sup>
(b) (4)	Drug Substance manufacturing and in-process/release testing	(b) (4)	IND 150440	Eli Lilly and Company	(b) (4)	Acceptable <sup>2</sup>
Eli Lilly Kinsale (FEI 3002806888)	Drug substance manufacturing and in-process/release testing	Kinsale, Ireland	IND 150440	Eli Lilly and Company	09/12/2018	Acceptable



Eli Lilly and Company (FEI 1819470)	Drug product manufacturing, in-process, release, and stability testing	Indianapolis, IN	IND 150440	Eli Lilly and Company	03/16/2021	Acceptable
(b) (4)	Drug product manufacturing, packaging, and labeling, and in-process and release testing	(b) (4)	IND 150440	Eli Lilly and Company	(b) (4)	Acceptable
Lilly France (FEI 3002807475)	Drug Product manufacturing and in-process testing	Fegersheim, France	IND 150440	Eli Lilly and Company	02/19/2019	Acceptable
(b) (4)	Drug substance and drug product release/stability testing	(b) (4)	IND 150440	Eli Lilly and Company	(b) (4)	Acceptable
(b) (4)	Adventitious virus testing of (b) (4)	(b) (4)	IND 150440	Eli Lilly and Company		Acceptable

1. Acceptable with specific required mitigation conditions of the authorization; Refer to OMQ memo in CMS [Case 611032 regarding Imclone](#).

2. A 704(a)(4) record review and virtual audit *in lieu* of an on-site inspection was conducted on Plant 3 of (b) (4). The facility was deemed acceptable to support bamlanivimab DS manufacture for the purpose of the EUA.

**Table 22: Manufacturing and testing Sites for Etesevimab**

Manufacturing Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant	Inspection Dates	GMP Status (if known)
Eli Lilly and Company (FEI 1819470)	Drug substance and drug product manufacturing, and in-process, release, and stability testing	Indianapolis, IN	IND 150707	Eli Lilly and Company	03/16/2021	Acceptable
(b) (4)	Drug Substance manufacturing and in-process/release testing	(b) (4)	IND 150707	Eli Lilly and Company	(b) (4)	Acceptable <sup>1</sup>
Lilly France (FEI 3002807475)	Drug Product manufacturing and in-process testing	Fegersheim, France	IND 150707	Eli Lilly and Company	02/19/2019	Acceptable

(b) (4)	Drug substance and drug product manufacturing, and in-process, release, and stability testing	(b) (4)	IND 150707	Eli Lilly and Company	(b) (4)	Acceptable
	Drug substance and drug product release/stability testing		IND 150707	Eli Lilly and Company		Acceptable
	Adventitious virus testing of (b) (4)		IND 150707	Eli Lilly and Company		Acceptable
	(b) (4)		IND 150707	Eli Lilly and Company		Acceptable

1. A 704(a)(4) record review and virtual audit *in lieu* of an on-site inspection was conducted on Plant 3 of (b) (4). The facility was deemed acceptable to support etesevimab DS manufacture for the purpose of the EUA.

## XVII. Clinical Trial Site Inspections

Clinical site inspections were not conducted for this EUA.

## XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

Nonclinical site inspections were not conducted for this EUA.

## XIX. Recommendations From Treatment Guidelines and Other Sources

At the time of writing of this review, there are no authorized or approved therapies for post-exposure prophylaxis following exposure to SARS-CoV-2. Casirivimab plus imdevimab (also known as REGEN-COV), two monoclonal antibodies directed against SARS-CoV-2, were authorized for emergency use for post-exposure prophylaxis for COVID-19 on July 30, 2021.

- The NIH COVID-19 Treatment Guidelines Panel issued a statement on the Emergency Use Authorization of Casirivimab plus Imdevimab as post-exposure for SARS-CoV-2 infection on August 17, 2021 (<https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-casirivimab-plus-imdevimab-as-pep/>). While vaccination remains the most effective way to prevent SARS-CoV-2 infection, it is noted that there are individuals who are either not fully vaccinated or cannot mount an adequate immune response to the vaccine. The Panel recommends the use of casirivimab 600 mg plus imdevimab 600 mg administered as subcutaneous injections or an intravenous infusion as post-exposure prophylaxis for people

who are at high risk for progression to severe COVID-19 as defined in EUA 91.

## **XX. Risk-Benefit Assessment and Recommendations for Emergency Use**

Bamlanivimab and etesevimab are recombinant neutralizing human IgG1 monoclonal antibodies that bind to different but overlapping epitopes in the receptor binding domain of the spike protein of SARS-CoV-2. Based on the review of results from Trial J2X-MC-PYAD, also called BLAZE-2 (NCT04497987), and in light of the known efficacy of bamlanivimab and etesevimab together in treating 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 progression to severe COVID-19, including hospitalization or death, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for post-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19 including hospitalization or death, and are not fully vaccinated<sup>1</sup> or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>), and have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC<sup>3</sup> or who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons). The known and potential benefits of bamlanivimab and etesevimab, administered together, outweigh the known and potential risks for the proposed authorized use.

The primary data supporting this authorization are from BLAZE-2, a Phase 3, randomized, double-blind, placebo-controlled trial in residents and staff of skilled nursing and assisted living facilities. Following the identification of an index case within a facility, participants were randomized to receive a single dose of placebo or bamlanivimab 4,200 mg. Overall, Trial PYAD Part 1 provided strong evidence that bamlanivimab prevented COVID-19 in skilled nursing and assisted living residents and staff. The primary endpoint for the Prevention Population was cumulative incidence of COVID-19, defined as the detection of SARS-CoV-2 by

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<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>

RT-PCR AND mild or worse disease severity within 21 days of detection, up to 8 weeks after randomization. In the Prevention Population, which consisted of all randomized participants who were SARS-CoV-2 RT-PCR negative and serology negative at baseline, the rate of mild or worse severity COVID-19 was 15% in the placebo arm and 9% in the bamlanivimab arm, which was highly statistically significant and corresponded with an estimated 40% reduction in rate of mild or worse severity COVID-19 through Week 8. The strongest evidence of benefit was in facility residents as well as a high risk subgroup that combined both residents and high risk facility staff. This high risk subgroup demonstrated a 70% reduction in risk of moderate or worse severity COVID-19 by Week 8. These data support the use of bamlanivimab and etesevimab for post-exposure prophylaxis of COVID-19, as described above.

Bamlanivimab 700 mg alone was originally authorized on November 9, 2020, 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. This authorization was ultimately revoked on April 16, 2021, as it was believed that known and potential benefits of bamlanivimab alone no longer outweighed the known and potential risks. Specifically, there was concern for the continued empiric use of bamlanivimab alone when, at that time, approximately 20% of the isolated SARS-CoV-2 sequences were resistant to bamlanivimab alone based on pseudotyped virus-like particle neutralization assay data.

Bamlanivimab 700 mg and etesevimab 1,400 mg are authorized for the treatment of 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 progression to severe COVID-19, including hospitalization and death. In Trial PYAB (BLAZE-1), a randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19, an 87% reduction in COVID-19 related hospitalizations or death was observed in the treatment group relative to placebo. Given the strong evidence that bamlanivimab 4,200 mg alone was effective in post-exposure prophylaxis for prevention of COVID-19 and that bamlanivimab 700 mg and etesevimab 1,400 mg administered together are effective for treatment of established COVID-19 infection to prevent progression of disease, it is reasonable to believe that bamlanivimab and etesevimab together may be used together for post-exposure prophylaxis to achieve similar prophylactic efficacy as bamlanivimab alone.

Regarding assessment of the known and potential risks, bamlanivimab and etesevimab both target the spike protein of the SARS-CoV-2 virus and both did not have any significant findings in the 3 week nonclinical toxicology studies nor any tissue binding of concern in the nonclinical GLP tissue cross-reactivity

studies. In general, administration of bamlanivimab and etesevimab has been well tolerated, however, similar to other monoclonal antibodies, infusion-related reactions, including the potential for anaphylaxis, are the most concerning safety events. As stated in the Fact Sheet for Health Care Providers for EUA 94, infusion-related reactions (n=16, 1.1%) and anaphylaxis (n=1, 0.07%) with bamlanivimab and etesevimab are rare when considering the 1,400 COVID-19 patients who have received an IV infusion of bamlanivimab and etesevimab at the authorized dose or higher in BLAZE-1 and BLAZE-4. In order to mitigate the risk of significant infusions reactions, patients should be clinically monitored for at least 1 hour after infusion is complete. Bamlanivimab and etesevimab should be administered in settings in which health care providers would 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.

The scope of the intended population for post-exposure prophylaxis is limited to individuals at high risk for progression to COVID-19 who are not fully vaccinated as defined by the CDC, or those who are not expected to mount an adequate response to complete SARS-CoV-2 vaccination. The CDC considers individuals to be fully vaccinated two weeks after their 2<sup>nd</sup> vaccine dose in a 2-dose series (e.g., the Pfizer or Moderna vaccines); or two weeks after a single-dose vaccine (such as the Johnson & Johnson's Janssen vaccine). Certain immunosuppressive conditions and immunosuppressive medications are reported to reduce antibody response to COVID-19 vaccination. The authorized use language in the Fact Sheet includes examples of these conditions and cites the CDC's website as a resource to guide the treating physicians who are considering the use of [REDACTED] prophylaxis in an individual expected to develop inadequate response to complete SARS-CoV-2 vaccination. To ensure correct use under EUA, the Limitations of Authorized Use specifies that bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

SEE ATTACHED  
ADDENDUM

The SARS-CoV-2 vaccines that are approved or authorized under EUA are the primary form of prevention; post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19, as communicated in the Limitations of Authorized Use statement in the Healthcare Provider Fact Sheet. Similar messaging is provided in the Fact Sheet for Patients, Parents and Caregivers under "what other prevention choices are there?".

Part 1 of BLAZE-2 was initiated prior to SARS-CoV-2 vaccine authorizations and did not enroll vaccinated individuals. As such, the effects of bamlanivimab and etesevimab on potential attenuation of vaccine response are not known at the present time. It is unclear how the administration of bamlanivimab and etesevimab together for post-exposure prophylaxis in an unvaccinated individual will affect the response to vaccination in the future.

Given the evolving nature of the SARS-CoV-2 variants in the United States, and because clinical samples that confirm a COVID-19 diagnosis are not typically sequenced prior to administration of these monoclonals, the clinical decision to use bamlanivimab and etesevimab together for post-exposure prophylaxis should be made in the context of what is known about local prevalence of the circulating variants at the time of use in order to avoid possible treatment or prevention failure. As such, a Limitations of Authorized Use for bamlanivimab and etesevimab, administered together, was added on August 27, 2021, to only authorize use in states, territories, and U.S. jurisdictions where combined frequency of variants resistant to bamlanivimab and etesevimab, administered together, is less than or equal to 5%.

B.1.617.2/Delta variant is now the dominant variant in the United States. The increase in prevalence of B.1.617.2 has been associated with a concomitant decrease in the frequency of identified variants that are expected to be resistant to bamlanivimab and etesevimab. Given this, as of September 2, 2021, bamlanivimab and etesevimab are now authorized for use for treatment in all 50 states, as well as in territories and U.S. jurisdictions, based on currently available data (see <https://www.fda.gov/media/151719/download> for complete list). It is therefore reasonable to authorize bamlanivimab and etesevimab for post-exposure prophylaxis in these locations as well. FDA, in collaboration with ASPR and CDC, will continue to monitor data as it becomes available and will update the list of states, territories, and U.S. jurisdictions in which bamlanivimab and etesevimab are authorized accordingly.

The FDA reviewed information on product quality including recent manufacturing facility inspectional history for both bamlanivimab and etesevimab. To address the specific CGMP deviations at the Imclone site, the letter of authorization will include specific conditions on quality and manufacturing that sufficiently address the risks associated with the production of bamlanivimab. These conditions include extra controls, additional verifications, and accelerated reporting mechanisms that ensure that each bamlanivimab drug substance batch is produced following CGMP as part of this emergency authorization. The conditions, among other things, also require that Lilly retain an independent third party (i.e., not affiliated with Lilly) to conduct a review of the batch records and any underlying data and associated discrepancies of bamlanivimab drug substance manufactured at Lilly Branchburg, NJ. Lilly will also retain an independent third-party (i.e., not affiliated with Lilly) to conduct laboratory release testing of bamlanivimab drug substance manufactured at Lilly Branchburg, NJ (excluding bioburden and endotoxin testing).

In sum, based on the totality of the scientific information available, including the efficacy of bamlanivimab 4,200 mg in preventing mild or worse COVID-19 in Trial PYAD (BLAZE-2) and the known efficacy of bamlanivimab 700 mg and etesevimab 1,400 mg in preventing COVID-19 hospitalization in patients with mild or moderate COVID-19, it is reasonable to believe that the authorized dose

of bamlanivimab 700 mg and etesevimab 1,400 mg administered together “may be effective” for the proposed authorized uses and the known and potential benefits outweigh the known and potential risks. Therefore, the Review Division and the Office of Infectious Diseases recommends extending the authorization of EUA94 for bamlanivimab 700 mg and etesevimab 1,400 mg to include post-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19 including hospitalization or death, and are not fully vaccinated<sup>1</sup> or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>), and have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC<sup>3</sup> or who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

## **XXI. Considerations for Adverse Event (AE) Monitoring**

This product will either be used in clinical trials or in clinical practice under EUA. Investigational product will be used in clinical trials conducted under IND. FDA IND safety reporting regulations will apply.

EUA-labeled product will be made available under the EUA. In the setting of a pandemic where practicing physicians will have many competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system.

The prescribing health care provider and/or the provider’s designee will be responsible for mandatory reporting of all medication errors and all serious adverse events considered to be potentially related to bamlanivimab and etesevimab occurring during bamlanivimab and etesevimab treatment within 7 calendar days from the onset of the event. The reports should include unique

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<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson’s Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>



identifiers and the words “bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA).”

## **XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA**

Refer to the Letter of Authorization and the authorized Fact Sheets for Health Care Providers.

## **XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product**

Fact sheets will be available to health care providers and patients through hard copy and/or electronic links.

The Applicant has indicated their plan for distribution of the Fact Sheet for Health Care Providers and Fact Sheet for Patients and Parents and Caregivers is as follows:

- One case will include 100 or 140 cartons of bamlanivimab or etesevimab. Each carton contains one vial of bamlanivimab 700 mg or one vial of etesevimab 700 mg and a leaflet with a QR code
  - The leaflet for bamlanivimab includes the global URL [www.bamlanivimabHCPinfo.com](http://www.bamlanivimabHCPinfo.com).
  - The leaflet for etesevimab includes the global URL [www.etesevimabHCPinfo.com](http://www.etesevimabHCPinfo.com).
  - Hard copies of the fact sheets will not be included but can be printed from the QR code or Global URL.
- The following URL is included on the label and carton of bamlanivimab: [www.bamlanivimabHCPinfo.com](http://www.bamlanivimabHCPinfo.com)
- The following URL is included on the label and carton of etesevimab: [www.etesevimabHCPinfo.com](http://www.etesevimabHCPinfo.com)
- These websites send the user to a single global labeling page, where a user can select country. Once the United States is selected, the user sees a pop-up where the user can access the Fact Sheets and Letter of Authorization directly from this pop-up box, or the user can get additional US-specific information by clicking on the link for [www.BAMandETE.com](http://www.BAMandETE.com) or [www.LillyAntibody.com](http://www.LillyAntibody.com)

FDA agrees with the plan for implementation for dissemination of the Fact Sheets.

- Fact Sheet for Health Care Providers (See Section XXVI. Appendices)

## **XXIV. Outstanding Issues/Data Gaps**

Not applicable.



## **XXV. References**

References are included in the relevant sections of this review, where applicable.

## **XXVI. Appendices**

1. Fact Sheet for Health Care Providers
2. Fact Sheet for Patients and Parent/Caregivers

# Appendix 1. Fact Sheet for Health Care Providers

## FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETESEVIMAB

### AUTHORIZED USE

#### TREATMENT

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab and etesevimab 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 progression to severe COVID-19, including hospitalization or death.

#### Limitations of Authorized Use

##### *Combined Frequency of Variants Resistant to Bamlanivimab and Etesevimab*

- Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.<sup>1</sup>
  - A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website: <https://www.fda.gov/media/151719/download>

##### *Use in Patients Who Are Hospitalized or Who Require Oxygen Due to COVID-19*

- Bamlanivimab and etesevimab 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 has not been studied 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.

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<sup>1</sup> FDA will make this determination considering current variant frequency data (available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

## **POST-EXPOSURE PROPHYLAXIS**

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk of progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated<sup>1</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>3</sup> **or**
- who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) [see *Limitations of Authorized Use (1.2)*].

### **Limitations of Authorized Use**

- Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.<sup>4</sup>
  - A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website: <https://www.fda.gov/media/151719/download>
- Post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19.
- Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

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<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>.

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>.

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>.

<sup>4</sup> FDA will make this determination considering current variant frequency data (available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

## RECENT MAJOR CHANGES

- |                                                                                                                                                                                                                                                                                          |                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| • <u>Authorized Use (Box and Section 1)</u> – addition of new indication for post-exposure prophylaxis of COVID-19.                                                                                                                                                                      | Revised 09/2021                       |
| • <u>Clinical Trial Results and Supporting Data for EUA, Post-Exposure Prophylaxis of COVID-19 (BLAZE-2) (Section 18.2)</u> – addition of Phase 3 data for the authorized use.                                                                                                           | Revised 09/2021                       |
| • <u>Authorized Use (Box and Section 1)</u> – expanded the definition of progression of severe COVID-19 to include death.                                                                                                                                                                | Revised 08/2021                       |
| • <u>Limitations of Authorized Use (Box and Section 1)</u> – change to authorized use related to the combined frequency of SARS-CoV-2 variants that are resistant to bamlanivimab and etesevimab.                                                                                        | Revised 08/2021                       |
| • <u>Antiviral Resistance (Box and Section 15)</u> – addition of information on susceptibility of SARS-CoV-2 variants to bamlanivimab and etesevimab (Table 3 and Table 4) and updates based on latest viral surveillance report and additional sequencing data from Phase 3 study PYAB. | Revised 08/2021, 05/2021, and 03/2021 |
| • <u>Warnings: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions (Section 5.1)</u> – addition of vasovagal reactions.                                                                                                                                                | Revised 08/2021                       |
| • <u>Warnings: Clinical Worsening After Bamlanivimab and Etesevimab Administration (Section 5.2)</u> – updated to include administration with both antibodies.                                                                                                                           | Revised 08/2021                       |
| • <u>Definition of High Risk for Disease Progression (Box and Section 2.1)</u> – definition has been expanded to include additional medical conditions and other factors.                                                                                                                | Revised 05/2021                       |
| • <u>Dosage and Administration, Dosage (Section 2.2)</u> – removal of rationale for authorized dose because Phase 3 data have confirmed the authorized dose.                                                                                                                             | Revised 05/2021                       |
| • <u>Overall Safety Summary, Clinical Trials Experience (Section 6.1)</u> – updated to integrated clinical trial safety analyses focused on adverse reactions and most common treatment-emergent adverse events.                                                                         | Revised 05/2021                       |
| • <u>Clinical Trial Results and Supporting Data for EUA, Mild to Moderate COVID-19 (BLAZE-1) (Section 18.1)</u> – addition of Phase 3 data for the authorized dose.                                                                                                                      | Revised 05/2021                       |

Bamlanivimab and etesevimab have been authorized by FDA for the emergency uses described above.

Bamlanivimab and etesevimab are not FDA-approved for these uses.

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

### **Treatment**

This EUA is for the use of the unapproved products bamlanivimab and etesevimab 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 progression to severe COVID-19, including hospitalization or death [see *Limitations of Authorized Use* (1.1)].

### **Post-Exposure Prophylaxis**

This EUA is for the use of the unapproved products bamlanivimab and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated<sup>1</sup> or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>) and
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>3</sup> or
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) [see *Limitations of Authorized Use* (1.2)].

### **Criteria for Identifying High Risk Individuals**

The following medical conditions or other factors may place adults and pediatric patients (12 years of age and older weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m<sup>2</sup>, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](https://www.cdc.gov/growthcharts/clinical_charts.htm))
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)

- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website:

<https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

### **SARS-CoV-2 Viral Variants**

- Review travel and contact history within 2 weeks prior to infection or exposure to SARS-CoV-2. Persons who have traveled to, resided in, or had close contact with an infected individual from an area where the frequency of resistant variants to bamlanivimab and etesevimab exceeds 5% should not receive bamlanivimab and etesevimab. Other monoclonal antibody therapy options should be considered.
- There are other authorized monoclonal antibody treatments available and healthcare providers should choose an authorized therapeutic option with activity against the circulating variants in their state, territory, or US jurisdiction.
- Healthcare providers should also refer to Section 15 of this Fact Sheet for further details regarding specific variants and resistance.

**Under this EUA, bamlanivimab and etesevimab must be administered together after dilution by intravenous (IV) infusion only.**

### **Treatment Dosage**

- The authorized dosage is 700 mg bamlanivimab and 1,400 mg of etesevimab administered together as a single intravenous (IV) infusion as soon as possible after positive viral test for SARS-CoV-2 and within ten days of symptom onset [see *Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18.1)*].

<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>.

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>.

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>.

### **Post-Exposure Prophylaxis Dosage**

- The authorized dosage is 700 mg bamlanivimab and 1,400 mg of etesevimab administered together as a single intravenous (IV) infusion as soon as possible after exposure to SARS-CoV-2.
- The authorized dosage is based on the totality of the scientific evidence including clinical pharmacology data and clinical trial data [see *Clinical Pharmacology* (14.2) and *Clinical Trial Results and Supporting Data for EUA* (18.2)].
- The clinical data for post-exposure prophylaxis is based on data generated in the Phase 3 study BLAZE-2. While this study only evaluated dosing with bamlanivimab alone, it is reasonable to expect that bamlanivimab and etesevimab together may be safe and effective for post-exposure prophylaxis based on:
  - Phase 3 data from BLAZE-1 demonstrated treatment of COVID-19 with bamlanivimab and etesevimab together showed a statistically significant reduction in progression of severe COVID-19, including hospitalization or death [see *Clinical Trial Results and Supporting Data for EUA* (18.1)].
  - Nonclinical and clinical data support that bamlanivimab and etesevimab together will provide an advantage over bamlanivimab alone against certain SARS-CoV-2 viral variants [see *Microbiology/Resistance Information* (15)].
- Use of bamlanivimab and etesevimab together for post-exposure prophylaxis in subjects who meet high-risk criteria is based on a subgroup analysis of high-risk individuals enrolled in BLAZE-2 [see *Clinical Trial Results and Supporting Data for EUA* (18.2)].

### **Intravenous Infusion:**

- Bamlanivimab and etesevimab are both available as solutions in separate vials and must be diluted and combined prior to administration.
- To prepare the dose you will need 1 vial of bamlanivimab and 2 vials of etesevimab.
- Administer bamlanivimab and etesevimab together as a single intravenous (IV) infusion via pump or gravity (see **Table 1** and **Table 2**).
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Bamlanivimab and etesevimab 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 bamlanivimab and etesevimab. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

Patients treated with bamlanivimab and etesevimab together 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 bamlanivimab and etesevimab in COVID-19, please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### Contraindications

None.

### Dosing

### **BAMLANIVIMAB AND ETESEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.**

#### Patient Selection for Treatment and Post-Exposure Prophylaxis

This section provides essential information on the unapproved products bamlanivimab and etesevimab administered together in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death for:

- Treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing [see *Limitations of Authorized Use* (1.1)].
- Post-exposure prophylaxis of COVID-19 in high risk individuals who are:
  - not fully vaccinated<sup>1</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>) **and**
    - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>3</sup> **or**
    - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in

<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>.

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>.

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>.



other individuals in the same institutional setting (for example, nursing homes, prisons) [see *Limitations of Authorized Use* (1.2)].

#### Criteria for Identifying High Risk Individuals

The following medical conditions or other factors may place adults and pediatric patients (12 years of age and older weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age  $\geq 65$  years of age)
- Obesity or being overweight (for example, adults with BMI  $> 25$  kg/m<sup>2</sup>, or if age 12-17, have BMI  $\geq 85$ th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](https://www.cdc.gov/growthcharts/clinical_charts.htm))
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

#### Dosage

##### Treatment:

The dosage in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

##### Post-Exposure Prophylaxis:

The dosage in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is 700 mg bamlanivimab and 1,400 mg etesevimab administered together as soon as possible following exposure to SARS-CoV-2.

### Dosage Adjustment in Specific Populations

No dosage adjustment is recommended based on age, sex, race, body weight, renal or mild hepatic impairment, during pregnancy or while lactating, or for disease severity or inflammation [see *Full EUA Prescribing Information, Use in Specific Populations (11)*].

### **Preparation and Administration**

#### Preparation

Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile prefilled infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1** and **Table 2**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab 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.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 1** or **Table 2**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

#### Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set.
  - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.

- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1 for patients weighing ≥50 kg** or **Table 2 for patients weighing <50 kg**). 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 bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

**Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion<sup>a</sup> in Patients Weighing 50 kg or More**

Drug <sup>a</sup> : Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Maximum Infusion Rate	Minimum Infusion Time
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL	310 mL/hr	60 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

**Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing Less Than 50 kg**

Drug <sup>a</sup> : Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total 60 mL to an infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Maximum Infusion Rate	Minimum Infusion Time
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL <sup>b</sup>	266 mL/hr	70 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

<sup>b</sup> The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

### Storage

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze, shake, or expose to direct light.

### Warnings

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

#### Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab and etesevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of bamlanivimab and etesevimab together. 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, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of bamlanivimab and etesevimab under Emergency Use Authorization.

#### Clinical Worsening After Bamlanivimab and Etesevimab Administration

Clinical worsening of COVID-19 after administration of bamlanivimab and etesevimab together 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 and etesevimab use or were due to progression of COVID-19.

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

Treatment with bamlanivimab and etesevimab has not been studied 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. Therefore, bamlanivimab and etesevimab are not authorized for use in patients [see *Limitations of Authorized Use* (1.1)]:

- 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 bamlanivimab and etesevimab [see *Full EUA Prescribing Information, Overall Safety Summary* (6.1)].

Additional adverse events associated with bamlanivimab and etesevimab, some of which may be serious, may become apparent with more widespread use.

#### **INSTRUCTIONS FOR HEALTHCARE PROVIDERS**

As the healthcare 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 bamlanivimab and etesevimab, including:

- FDA has authorized the emergency use of bamlanivimab and etesevimab 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 progression to severe COVID-19, including hospitalization or death [see *Limitations of Authorized Use* (1.1)].
- FDA has authorized the emergency use of bamlanivimab and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in

individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated<sup>1</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>3</sup> **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) [see *Limitations of Authorized Use* (1.2)].
- The patient or parent/caregiver has the option to accept or refuse bamlanivimab and etesevimab.
- The significant known and potential risks and benefits of bamlanivimab and etesevimab, and the extent to which such potential risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with bamlanivimab and etesevimab together 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 bamlanivimab and etesevimab together for COVID-19, please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

#### **MANDATORY REQUIREMENTS FOR BAMLANIVIMAB AND ETESEVIMAB ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:**

In order to mitigate the risks of using these unapproved products and to optimize the potential benefit of bamlanivimab and etesevimab under this EUA, the following items are required. Use of bamlanivimab and etesevimab 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 progression

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<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>.

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>.

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>.

- to severe COVID-19, including hospitalization or death [see *Limitations of Authorized Use (1.1)*].
2. Post-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:
    - a. not fully vaccinated<sup>1</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>) **and**
      - i. have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>3</sup> **or**
      - ii. who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) [see *Limitations of Authorized Use (1.2)*].
  3. As the healthcare 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 bamlanivimab and etesevimab. Healthcare 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 authorized bamlanivimab and etesevimab, and
    - c. Informed that bamlanivimab and etesevimab are unapproved drugs that are authorized for use under this Emergency Use Authorization.
  4. Patients with known hypersensitivity to any ingredient of bamlanivimab or etesevimab must not receive bamlanivimab and etesevimab.
  5. The prescribing health care provider and/or the provider’s designee is/are responsible for mandatory reporting of all medication errors and serious adverse events\* potentially related to bamlanivimab and etesevimab treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words “bamlanivimab and

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<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson’s Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>.

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>.

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>.



etesevimab 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](http://www.fda.gov/medwatch/report.htm), or
  - Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by:
    - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
    - 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” the statement “bamlanivimab and etesevimab 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. The prescribing health care provider and/or the provider’s designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of bamlanivimab and etesevimab.
7. 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:  
Eli Lilly and Company, Global Patient Safety  
Fax: 1-317-277-0853  
E-mail: [mailindata\\_gsmtindy@lilly.com](mailto:mailindata_gsmtindy@lilly.com)  
Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.



## APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

There is no adequate, approved and available alternative to bamlanivimab and etesevimab administered together for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated<sup>1</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>2</sup>) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>3</sup> **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) [see *Limitations of Authorized Use* (1.2)].

Additional information on COVID-19 therapies 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 Eli Lilly and Company for the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at

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<sup>1</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>.

<sup>2</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>.

<sup>3</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>.

least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.<sup>1</sup>

FDA has also issued this EUA, requested by Eli Lilly and Company for the unapproved products bamlanivimab and etesevimab administered together in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk of progression to severe COVID-19, including hospitalization or death, and are:

- not fully vaccinated<sup>2</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>3</sup>) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>4</sup> **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons) [see *Limitations of Authorized Use* (1.2)].

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for the treatment of mild to moderate COVID-19 or for post-exposure prophylaxis of COVID-19 in individuals 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 bamlanivimab and etesevimab 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.

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<sup>1</sup> The health care provider should visit [clinicaltrials.gov](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.

<sup>2</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>.

<sup>3</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>.

<sup>4</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>.

As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

**CONTACT INFORMATION**

For additional information visit

[www.LillyAntibody.com](http://www.LillyAntibody.com)

If you have questions, please contact  
1-855-LillyC19 (1-855-545-5921)

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**END SHORT VERSION FACT SHEET**  
**Long Version Begins on Next Page**

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# FULL EUA PRESCRIBING INFORMATION

## FULL EUA PRESCRIBING INFORMATION: CONTENTS\*

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

## 1 AUTHORIZED USE

### 1.1 TREATMENT

Bamlanivimab and etesevimab administered together are authorized for use under an EUA 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 progression to severe COVID-19, including hospitalization or death.

#### Limitations of Authorized Use

##### Combined Frequency of Variants Resistant to Bamlanivimab and Etesevimab

- Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.<sup>43</sup>
  - A list of states, territories, and other US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website: <https://www.fda.gov/media/151719/download>

##### Use in Patients Who Are Hospitalized or Who Require Oxygen Due to COVID-19

- Bamlanivimab and etesevimab 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 has not been studied 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 [see *Warnings and Precautions* (5.3)].

### 1.2 POST-EXPOSURE PROPHYLAXIS

Bamlanivimab and etesevimab administered together are authorized for use under an EUA for post-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age or older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

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<sup>43</sup> FDA will make this determination considering current variant frequency data (available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

- not fully vaccinated<sup>44</sup> **or** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications<sup>45</sup>) **and**
  - have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)<sup>46</sup> **or**
  - who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

## Limitations of Authorized Use

- Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%.<sup>47</sup>
  - A list of states, territories, and other US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website: <https://www.fda.gov/media/151719/download>
- Post-exposure prophylaxis with bamlanivimab and etesevimab is not a substitute for vaccination against COVID-19.
- Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Patient Selection

The following medical conditions or other factors may place adults and pediatric patients (12 years of age and older weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m<sup>2</sup>, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, [https://www.cdc.gov/growthcharts/clinical\\_charts.htm](https://www.cdc.gov/growthcharts/clinical_charts.htm))
- Pregnancy
- Chronic kidney disease
- Diabetes

<sup>44</sup> Individuals are considered to be fully vaccinated 2 weeks after their second vaccine dose in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine). See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html#vaccinated>.

<sup>45</sup> See this website for more details: <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html>.

<sup>46</sup> Close contact with an infected individual is defined as: being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected person (sneezing or coughing, for example). See this website for additional details: <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>.

<sup>47</sup> FDA will make this determination considering current variant frequency data (available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>), trends in variant frequency over time, the precision of the estimates and information regarding emerging variants of concern. FDA will update the list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized as new data and information becomes available. Healthcare providers should refer to the FDA website regularly for updates.

- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

## 2.2 Dosage

Treatment:

The dosage in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is bamlanivimab 700 mg and etesevimab 1,400 mg administered together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Post-Exposure Prophylaxis:

The dosage in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) is 700 mg bamlanivimab and 1,400 mg etesevimab administered together as a single intravenous infusion. Bamlanivimab and etesevimab should be given together as soon as possible following exposure to SARS-CoV-2.

Under this EUA, bamlanivimab and etesevimab must be diluted and administered together as a single intravenous infusion.

## 2.3 Dosage 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 12 years of age and older. Bamlanivimab and etesevimab are not authorized for

patients weighing less than 40 kg or those less than 12 years of age [see *Use in Specific Populations* (11.3)].

#### Geriatric Use

No dosage adjustment is recommended in geriatric patients [see *Use in Specific Populations* (11.4)].

#### Renal Impairment

No dosage adjustment is recommended in patients with renal impairment [see *Use in Specific Populations* (11.5)].

#### Hepatic Impairment

No dosage adjustment is recommended in patients with mild hepatic impairment. Bamlanivimab and etesevimab has not been studied in patients with moderate or severe hepatic impairment [see *Use in Specific Populations* (11.6)].

## **2.4 Dose Preparation and Administration**

### Preparation

Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-line PVC, sterile infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1** and **Table 2**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab 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.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 1** or **Table 2**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.



## Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set
  - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1 for patients weighing ≥50 kg** or **Table 2 for patients weighing <50 kg**). 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 bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

**Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion<sup>a</sup> in Patients Weighing 50 kg or More**

Drug <sup>a</sup> : Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Maximum Infusion Rate	Minimum Infusion Time
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL	310 mL/hr	60 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

**Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion<sup>a</sup> in Patients Weighing Less Than 50 kg**

Drug <sup>a</sup> : Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	Maximum Infusion Rate	Minimum Infusion Time

50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL <sup>b</sup>	266 mL/hr	70 minutes

<sup>a</sup> 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

<sup>b</sup> The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

## **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 infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

## **3 DOSAGE FORMS AND STRENGTHS**

Bamlanivimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as:

- Injection: 700 mg/20 mL (35 mg/mL) as in a single-dose vial.

Etesevimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as:

- Injection: 700 mg/20 mL (35 mg/mL) in a single-dose vial.

## **4 CONTRAINDICATIONS**

None.

## **5 WARNINGS AND PRECAUTIONS**

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

### **5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions**

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab and etesevimab. 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, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of bamlanivimab and etesevimab together. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include [see *Overall Safety Summary* (6.1)]:

- 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, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of bamlanivimab and etesevimab under Emergency Use Authorization.

## **5.2 Clinical Worsening After Bamlanivimab and Etesevimab Administration**

Clinical worsening of COVID-19 after administration of bamlanivimab and etesevimab together 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 and etesevimab use or were due to progression of COVID-19.

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

Treatment with bamlanivimab and etesevimab has not been studied 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. Therefore, bamlanivimab and etesevimab are not authorized for use in patients [see *Limitations of Authorized Use* (1.1)]:

- 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**

## **6.1 Clinical Trials Experience**

The safety of bamlanivimab administered with etesevimab is primarily based on exposure of approximately 1,400 ambulatory (non-hospitalized) subjects who received doses of bamlanivimab and etesevimab together, at the recommended dose or higher, in BLAZE-1 and BLAZE-4. BLAZE-1 is a Phase 2/3, randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19. In the Phase 3 portion of the trial, enrolled participants had at least one risk factor for the development of severe COVID-19 illness. BLAZE-4 is a Phase 2, randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab for the treatment of subjects with mild to moderate COVID-19. Subjects  $\geq 65$  years old or with BMI  $\geq 35$  were excluded from enrollment. In clinical trials, approximately 4,000 subjects have received

bamlanivimab (either alone or with etesevimab) at doses ranging from 700 to 7,000 mg. Bamlanivimab and etesevimab at the authorized doses of 700 mg and 1,400 mg have been administered together to approximately 800 subjects in clinical trials [see *Clinical Pharmacology* (14.2)].

The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received bamlanivimab and etesevimab together at the authorized dose or higher [see *Warnings and Precautions* (5.1)]:

- anaphylaxis (n=1, 0.07%)
- infusion-related reactions (n=16, 1.1%)

In the case of anaphylaxis and serious infusion-related reactions, all infusions were stopped, and treatment was administered. One case required epinephrine. All events resolved.

The most common treatment-emergent adverse events in the bamlanivimab and etesevimab treatment group in BLAZE-1 and BLAZE-4 included nausea, dizziness, and pruritus. No treatment-emergent adverse events occurred in more than 1% of participants and the rates were comparable in the treatment and placebo groups.

## **7 PATIENT MONITORING RECOMMENDATIONS**

Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete [see *Warnings and Precautions* (5.1) and *Overall Safety Summary* (6.1)].

## **8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS**

Clinical trials evaluating the safety of bamlanivimab and etesevimab are ongoing [see *Overall Safety Summary* (6)].

Completion of FDA MedWatch Form to report all medication errors and serious adverse events\* occurring during bamlanivimab and etesevimab use and considered to be potentially related to bamlanivimab and etesevimab 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 bamlanivimab and etesevimab under this EUA, the prescribing healthcare 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](http://www.fda.gov/medwatch/report.htm), or
- Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - 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 adverse events and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of bamlanivimab and etesevimab
- 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
3. In section B, box 5, description of the event:
  - a. Write "bamlanivimab and etesevimab 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 healthcare provider or institutional designee who is responsible for the report.
  - b. Provide the address of the treating institution (NOT the healthcare 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:  
Eli Lilly and Company, Global Patient Safety  
Fax: 1-317-277-0853  
E-mail: [mailindata\\_gsmtindy@lilly.com](mailto:mailindata_gsmtindy@lilly.com)  
Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

## 10 DRUG INTERACTIONS

Bamlanivimab and etesevimab 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. Bamlanivimab and etesevimab 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 performed with bamlanivimab or etesevimab. In tissue cross reactivity studies using human fetal tissues, no binding of clinical concern was detected for etesevimab or bamlanivimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bamlanivimab and etesevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bamlanivimab or etesevimab 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 bamlanivimab or etesevimab in human or animal milk, the effects on the breastfed infant, or the effects 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 bamlanivimab and etesevimab and any potential adverse effects on the breastfed child from bamlanivimab and etesevimab 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**

Bamlanivimab and etesevimab are not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of bamlanivimab and etesevimab administered together are being assessed in adolescent patients in ongoing clinical trials. The PK of bamlanivimab 700 mg and etesevimab 1,400 mg has been evaluated in pediatric patients ages 12 years or older who weigh at least 40 kg. The data show that the plasma exposures in these 10 patients are comparable to

what has been observed in adult patients at the authorized dose. The PK of bamlanivimab and etesevimab has not been evaluated in pediatric patients ages <12 years who weigh <40 kg.

#### **11.4 Geriatric Use**

Of the 1141 patients receiving bamlanivimab and etesevimab in BLAZE-1, 30% were 65 years of age and older and 10% were 75 years of age and older. Based on population PK analyses, there is no difference in PK of bamlanivimab or etesevimab in geriatric patients compared to younger patients [see *Clinical Trial Results and Supporting Data for EUA (18.1)*].

#### **11.5 Renal Impairment**

Bamlanivimab and etesevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of bamlanivimab or etesevimab.

#### **11.6 Hepatic Impairment**

Based on population PK analysis, there is no difference in PK of bamlanivimab or etesevimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bamlanivimab and etesevimab have not been studied in patients with moderate or severe hepatic impairment.

#### **11.7 Other Specific Populations**

Based on population PK analysis, the PK of bamlanivimab and etesevimab was not affected by sex, race, or disease severity. Body weight had no clinically relevant effect on the PK of bamlanivimab and etesevimab in adults with COVID-19 over the body weight range of 41 kg to 173 kg.

### **12 OVERDOSAGE**

Doses up to 7,000 mg of bamlanivimab (10 times the authorized dose of bamlanivimab) or 7,000 mg of etesevimab (5 times the authorized dose of etesevimab) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose with bamlanivimab and etesevimab 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 either bamlanivimab or etesevimab.

### **13 DESCRIPTION**

#### **Bamlanivimab**

Bamlanivimab is a human immunoglobulin G-1 (IgG1 variant) monoclonal antibody consisting of 2 identical light chain polypeptides composed of 214 amino acids each and 2 identical heavy chain polypeptides composed of 455 amino acids produced by a Chinese Hamster Ovary (CHO) cell line and molecular weight of 146 kDa.

Bamlanivimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous infusion after dilution.

Each mL contains 35 mg of bamlanivimab, and L-histidine (0.4 mg), L-histidine hydrochloride monohydrate (0.6 mg), sodium chloride (2.9 mg), sucrose (60 mg), polysorbate 80 (0.5 mg), and Water for Injection. The bamlanivimab solution has a pH range of 5.5-6.5.

#### Etesevimab

Etesevimab is a human IgG1 variant monoclonal antibody (mAb) consisting of 2 identical light chain polypeptides composed of 216 amino acids each and 2 identical heavy chain polypeptides composed of 449 amino acids produced by a Chinese Hamster Ovary (CHO) cell line and molecular weight of 145 kDa.

Etesevimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous infusion after dilution.

Each mL contains 35 mg of etesevimab, L-histidine (1.55 mg), L-histidine hydrochloride monohydrate (2.10 mg), sucrose (80.4 mg), polysorbate 80 (0.5 mg), and Water for injection. The etesevimab solution has a pH range of 5.5.-6.5.

## **14 CLINICAL PHARMACOLOGY**

### **14.1 Mechanism of Action**

Bamlanivimab is a recombinant neutralizing human IgG1k monoclonal antibody (mAb) to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. Bamlanivimab binds the spike protein with a dissociation constant  $K_D = 0.071$  nM and blocks spike protein attachment to the human ACE2 receptor with an  $IC_{50}$  value of 0.17 nM (0.025 µg/mL).

Etesevimab is a recombinant neutralizing human IgG1k mAb to the spike protein of SARS-CoV-2, with amino acid substitutions in the Fc region (L234A, L235A) to reduce effector function. Etesevimab binds the spike protein with a dissociation constant  $K_D = 6.45$  nM and blocks spike protein attachment to the human ACE2 receptor with an  $IC_{50}$  value of 0.32 nM (0.046 µg/mL).

Bamlanivimab and etesevimab bind to different but overlapping epitopes in the receptor binding domain (RBD) of the S-protein. Using both antibodies together is expected to reduce the risk of viral resistance.

### **14.2 Pharmacodynamics**

A flat exposure-response relationship for efficacy was identified for bamlanivimab and etesevimab administered together within the dose range of 700 mg bamlanivimab and 1,400 mg etesevimab to 2,800 mg bamlanivimab and 2,800 mg etesevimab (4 and 2 times the authorized dose, respectively), based on clinical data and pharmacokinetic/pharmacodynamic modeling.

For post-exposure prophylaxis of COVID-19, a dose of 700 mg bamlanivimab and 1,400 mg etesevimab was supported based on clinical data and pharmacokinetic/pharmacodynamic modeling.

### **14.3 Pharmacokinetics**

Pharmacokinetic profiles of bamlanivimab and etesevimab are linear and dose-proportional between 700 mg and 7000 mg following a single IV administration. There were no differences in



PK of bamlanivimab between severe/moderate participants who were hospitalized and mild/moderate ambulatory participants. There were no differences in PK of etesevimab between mild/moderate ambulatory participants and healthy participants. There is no change in PK of bamlanivimab or etesevimab administered alone or together suggesting there is no interaction between the two antibodies.

### Absorption

The mean maximum concentration (C<sub>max</sub>) of 700 mg bamlanivimab was 196 µg/mL (90% CI: 102 to 378 µg/mL) following approximately 1 hour 700 mg IV infusion.

The mean maximum concentration (C<sub>max</sub>) of 1400 mg etesevimab is estimated to be 504 µg/mL (90% CI: 262 to 974 µg/mL) following approximately 1 hour IV infusion.

### Distribution

Bamlanivimab mean volume of distribution (V) was 2.87 L and 2.71 L for the central and peripheral compartments, respectively. The between subject variability was 23.2% CV.

Etesevimab mean volume of distribution (V) was 2.38 L and 1.98 L for the central and peripheral compartments, respectively. The between subject variability was 27.8% CV.

### Metabolism

Bamlanivimab and etesevimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

### Elimination

Bamlanivimab clearance (CL) was 0.27 L/day (between subject variability 22.3% CV) and the mean apparent terminal elimination half-life was 17.6 days (between subject variability 15.8% CV). Following a single 700 mg IV dose, bamlanivimab was quantifiable for at least 29 days. The mean concentration was 22 µg/mL (90% CI: 10.7 to 41.6 µg/mL) on Day 29.

Etesevimab clearance (CL) was 0.128 L/day (between subject variability 33.8% CV) and the mean apparent terminal elimination half-life was 25.1 days (between subject variability 29.2% CV). Following a single 1,400 mg IV dose, etesevimab was quantifiable for at least 29 days. The mean concentration was 111 µg/mL (90% CI: 57.4 to 199 µg/mL) on Day 29.

### Special Populations:

The PK profiles of bamlanivimab and etesevimab were not affected by age, sex, race, or disease severity based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bamlanivimab or etesevimab in adults with COVID-19 over the body weight range of 41 kg to 173 kg [see *Use in Specific Populations* (11.4, 11.7)].

#### *Pediatric population*

The PK of bamlanivimab and etesevimab at the authorized dose has been evaluated in 10 pediatric patients ages 12 years or older who weigh at least 40 kg. The data show that the plasma

exposures in these patients are comparable to what has been observed in adult patients. The PK of bamlanivimab and etesevimab has not been evaluated in pediatric patients ages <12 years who weigh <40 kg.

#### *Patients with renal impairment*

Bamlanivimab and etesevimab are not eliminated intact in the urine. Renal impairment is not expected to impact the PK of bamlanivimab and etesevimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of bamlanivimab and etesevimab [see *Use in Specific Populations* (11.5)].

#### *Patients with hepatic impairment*

Based on population PK analysis, there is no significant difference in PK of bamlanivimab or etesevimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bamlanivimab and etesevimab have not been studied in patients with moderate or severe hepatic impairment [see *Use in Specific Populations* (11.6)].

#### Drug interactions:

Bamlanivimab and etesevimab 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.

## **15 MICROBIOLOGY/RESISTANCE INFORMATION**

### Antiviral Activity

The cell culture neutralization activity of bamlanivimab and of etesevimab against SARS-CoV-2 was measured in a dose-response model quantifying plaque reduction using cultured Vero E6 cells. Bamlanivimab, etesevimab and a 1:1 (weight/weight) ratio of bamlanivimab and etesevimab together neutralized the USA/WA/1/2020 isolate of SARS-CoV-2 with estimated EC<sub>50</sub> values = 0.14 nM (0.02 µg/mL), 0.97 nM (0.14 µg/mL) and 0.14 nM (0.02 µg/mL), respectively.

Bamlanivimab demonstrated antibody-dependent cell-mediated cytotoxicity on reporter Jurkat cells expressing FcγRIIIa following engagement with target cells expressing spike protein. Bamlanivimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

Etesevimab did not demonstrate detectable antibody-dependent cell-mediated cytotoxicity on Jurkat reporter cells expressing FcγRIIIa. Etesevimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

### Antibody Dependent Enhancement (ADE) of Infection

The risk that bamlanivimab and etesevimab could mediate viral uptake and replication by immune cells was studied in THP-1 and Raji cell lines and primary human macrophages. In general, experiments with bamlanivimab, with etesevimab, and with bamlanivimab and etesevimab together did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of mAb(s) down to at least 100-fold below the respective EC<sub>50</sub> value(s).

### Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab and/or etesevimab (Table 3).<sup>48</sup> There are other authorized monoclonal

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<sup>48</sup> A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the following FDA website: <https://www.fda.gov/media/151719/download>.

antibody treatments available and healthcare providers should choose an authorized therapeutic option with activity against circulating variants in their state, territory, or US jurisdiction. Variant frequency data for states, territories, and US jurisdictions can be accessed on the following CDC website: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>.

Resistant variants were identified using directed evolution of the spike protein and serial passage in cell culture of SARS-CoV-2 in the presence of bamlanivimab or etesevimab individually. Resistant variants were not identified when bamlanivimab and etesevimab were tested together using the same methodology. Viral variants identified in these studies that had reduced susceptibility to bamlanivimab included spike protein amino acid substitutions E484D/K/Q, F490S, Q493R, and S494P, and variants that had reduced susceptibility to etesevimab included substitutions K417N, D420N, and N460K/S/T/Y. Neutralization assays using SARS-CoV-2 and vesicular stomatitis virus (VSV) virus-like particles (VLP) pseudotyped with variant SARS-CoV-2 spike protein confirmed reductions in susceptibility to the selecting antibody. Retention of susceptibility to the other antibody alone was observed, with the exception of the E484D and Q493R substitution. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of those with E484D, E484K, E484Q, and Q493R substitutions, which had reduced susceptibility of 145-fold, 24-fold, 17-fold, and 1,054-fold, respectively in a pseudotyped VLP assay.

Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing. Pseudotyped VLP evaluation of amino acid substitutions identified in global surveillance showed that the V483A substitution reduced susceptibility to bamlanivimab 48-fold, but activity was maintained with etesevimab, and with bamlanivimab and etesevimab together. N501Y and N501T substitutions reduced susceptibility to etesevimab approximately 5-fold and 20-fold, respectively. Activity against variants with N501Y or N501T substitutions was maintained with bamlanivimab alone, and with bamlanivimab and etesevimab together.

Bamlanivimab and etesevimab together retained activity against a SARS-CoV-2 B.1.1.7 lineage (Alpha; UK origin) virus and related pseudotyped VLPs expressing the spike protein found in the B.1.1.7 variant (Tables 3 and 4). SARS-CoV-2 B.1.351 lineage (Beta; South Africa origin) virus and related pseudotyped VLPs expressing spike proteins from B.1.351 lineage or substitutions K417N + E484K + N501Y found in this lineage had reduced susceptibility to bamlanivimab and etesevimab together of >324, 431-fold or >45-fold, respectively. Pseudotyped VLPs expressing spike protein from the P.1 lineage (Gamma; Brazil origin) or K417T + E484K + N501Y found in the P.1 lineage had reduced susceptibility to bamlanivimab and etesevimab together of 252-fold or >3,351-fold, respectively.

Bamlanivimab and etesevimab together and etesevimab alone retained activity against SARS-CoV-2 B.1.617.2 lineage (Delta; India origin) virus and related pseudotyped VLPs, but bamlanivimab alone had reduced activity (>1,136 and >1,868-fold, respectively). Bamlanivimab and etesevimab are expected to retain activity against B.1.617.2 sublineage AY.3 (India origin). B.1.617.2 sublineages AY.1/AY.2 (commonly known as “Delta plus”; India origin) have an additional K417N substitution; pseudotyped VLPs expressing AY.1/AY.2 related spike sequence had a reduced susceptibility to bamlanivimab and etesevimab together of 1,235-fold. SARS-CoV-2 recombinant virus containing the L452R substitution present in B.1.427/B.1.429 lineages (Epsilon; USA [California] origin) and pseudotyped VLPs expressing the full-length spike protein or the L452R substitution found in this lineage showed reduced susceptibility to bamlanivimab and etesevimab together of 11-fold, 9-fold or 5-fold, respectively. Pseudotyped VLPs expressing spike protein from the B.1.617.1 lineage (Kappa; India origin) showed reduced susceptibility to

bamlanivimab and etesevimab together of 6-fold; for this variant, susceptibility to etesevimab alone was maintained, but not to bamlanivimab alone (>1,030-fold reduction). Bamlanivimab and etesevimab together and etesevimab alone retained activity against pseudotyped VLPs expressing the full-length spike protein from the C.37 lineage (Lambda; Peru origin), but bamlanivimab alone had reduced activity (>2,112-fold reduction). Pseudotyped VLPs expressing spike protein from the B.1.621 lineage (Mu; Colombia origin) show reduced susceptibility to bamlanivimab and etesevimab together of 116-fold, due to susceptibility reductions to bamlanivimab (>1,863-fold) and etesevimab (17-fold) alone.

**Table 3: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)**

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested <sup>a</sup>	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change <sup>b</sup>
B.1.351	South Africa	Beta	K417N + E484K + N501Y	431 <sup>c</sup>
P.1	Brazil	Gamma	K417T + E484K + N501Y	252 <sup>c</sup>
B.1.617.2/AY.3	India	Delta	L452R + T478K	no change <sup>b</sup>
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N] <sup>d</sup>	L452R + T478K + K417N	1,235 <sup>c</sup>
B.1.427/B.1.429	USA (California)	Epsilon	L452R	9 <sup>e</sup>
B.1.526 <sup>f</sup>	USA (New York)	Iota	E484K	30
B.1.617.1	India	Kappa	L452R + E484Q	6 <sup>e</sup>
C.37	Peru	Lambda	L452Q + F490S	no change <sup>b</sup>
B.1.621	Colombia	Mu	R346K + E484K + N501Y	116 <sup>c</sup>

<sup>a</sup> Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudoviruses containing the full-length spike protein reflective of the consensus sequence for each of the variant lineages were tested.

<sup>b</sup> No change: <5-fold reduction in susceptibility.

<sup>c</sup> Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage.

<sup>d</sup> Commonly known as "Delta plus."

<sup>e</sup> Etesevimab retains activity against this variant.

<sup>f</sup> Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

**Table 4: Authentic<sup>a</sup> SARS-CoV-2 Neutralization Data for Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)**

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested <sup>b</sup>	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	no change <sup>c</sup>
B.1.351	South Africa	Beta	K417N, E484K, N501Y	>325
B.1.617.2/AY.3	India	Delta	L452R, T478K	no change <sup>c</sup>
B.1.427/B.1.429	USA (California)	Epsilon	L452R	11
B.1.526 <sup>d</sup>	USA (New York)	Iota	E484K	11

<sup>a</sup> The B.1.1.7 variant was assessed using cell culture-expanded virus isolates and tested using an immunofluorescence based microneutralization assay and by plaque reduction assay; B.1.351 and B.1.617.2 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay; the B.1.526/E484K and B.1.427/B.1.429/L452R substitutions

were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate with E484K or L452R) and tested using a plaque reduction assay.

- <sup>b</sup> Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage.
- <sup>c</sup> No change: <5-fold reduction in susceptibility.
- <sup>d</sup> Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021). This assay was conducted using recombinant SARS-CoV-2 with the E484K substitution only.

Due to the large reduction of pseudotyped VLP neutralization activity of both bamlanivimab and etesevimab against the substitutions in B.1.351 (Beta; South Africa origin), P.1 (Gamma; Brazil origin), AY.1/AY.2 ("Delta plus"; India origin), and B.1.621 (Mu; Colombia origin), it is unlikely that bamlanivimab and etesevimab together will be active against these variants.

It is unclear how small reductions in susceptibility to bamlanivimab and etesevimab seen in authentic or recombinant SARS-CoV-2 or pseudotyped VLP assays correlate with clinical outcomes.

In authentic SARS-CoV-2 assays, bamlanivimab and etesevimab together retained activity against variants of B.1.1.7 (Alpha) and B.1.617.2/AY.3 (Delta) lineages (Table 4), although bamlanivimab alone had reduced activity to B.1.617.2/AY.3 (Delta) in this assay (>1,136-fold). SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the E484K substitution present in the B.1.526 lineage (Iota; USA [New York] origin) or the L452R substitution present in the B.1.427/B.1.429 lineage (Epsilon; USA [California] origin) showed reduced susceptibility to bamlanivimab and etesevimab together of 11-fold. Susceptibility to etesevimab alone was maintained for both isolates, but not to bamlanivimab alone (>833-fold and >1,460-fold reduction for E484K and L452R viruses, respectively). Available nonclinical and clinical PK data indicate that etesevimab at the authorized dose may retain activity against the B.1.526 variant clinically, although only very limited data are currently available from patients infected with this variant in clinical trials. Preliminary clinical evidence indicates that the administration of bamlanivimab and etesevimab together result in similar viral load reductions in participants infected with the L452R variant (Epsilon; USA [California] origin) as observed in those who were infected with bamlanivimab-sensitive strains. Of the 134 participants infected with the L452R variant at baseline in the Phase 3 portion of BLAZE-1, 3 of the 50 individuals treated with placebo (6%) and 1 of the 84 participants treated with bamlanivimab 700 mg and etesevimab 1,400 mg (1%) were hospitalized (p=0.15).

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab- and etesevimab-resistance associated spike variations in clinical trials. Analysis of baseline samples show that 8.4% (188/2246) of clinical trial patients were infected with viral variants containing single amino acid substitutions at positions associated with reduced susceptibility to either bamlanivimab or etesevimab as predicted by pseudotyped VLP or authentic SARS-CoV-2 neutralization assays. No patients were infected with a variant that was predicted to have reduced susceptibility to both bamlanivimab and etesevimab by these assessments.

Patient samples were also analyzed for treatment-emergent viral variants, defined as variants with single amino acid substitutions at positions that had reduced susceptibility to either bamlanivimab or etesevimab present at an allele fraction of ≥15%.

- In the Phase 3 portion of BLAZE-1, treatment-emergent variants were observed in 9.0% (42/467) of patients treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together, in 5.3% (21/394) of patients treated with bamlanivimab 700 mg and etesevimab 1,400 mg together, and in 4.0% (27/674) of patients treated with placebo. The majority of these were only detected at one time point in the sequential series with 0.9% (4/467), 1.0% (4/394), and 0.3% (2/674) of patients having multiple instances of detection in the

bamlanivimab 2,800 mg and etesevimab 2,800 mg together, bamlanivimab 700 mg and etesevimab 1,400 mg together, and placebo groups, respectively.

- In patients treated with bamlanivimab and etesevimab together, substitutions detected in one or more patients included ones with reduced susceptibility ( $\geq 5$ -fold) to bamlanivimab only: L452R/W, E484K, G485V, F490L, and S494P; and ones with reduced susceptibility to etesevimab only: D405G/Y, K417N, D420N/Y, N460H/I/T, A475S/V, Y489H, and N501I/Y. While these variants had reduced susceptibility to either bamlanivimab OR etesevimab compared to wild-type in a pseudotyped VSV VLP or authentic virus assay they still retained susceptibility to the other antibody in the combination.
- There were also observations of variants with reduced susceptibility ( $\geq 5$ -fold) to both bamlanivimab and etesevimab and to bamlanivimab + etesevimab tested together: E484D (n=1; 145-fold reduction to bamlanivimab + etesevimab tested together at a molar ratio of 1:2), Q493K/R (n=9; 584-fold and 1,054-fold reduction to bamlanivimab + etesevimab tested together at a molar ratio of 1:2 for Q493K and Q493R, respectively) out of a total of 861 patients treated with bamlanivimab and etesevimab together.
- In a subgroup of participants infected with virus harboring L452R substitution found in the B.1.427/B.1.429 (Epsilon) lineage, a S459P treatment-emergent substitution was identified in one subject. Concurrent L452R+S459P substitutions conferred a 1,656-fold reduction in susceptibility to bamlanivimab + etesevimab together (1:2 molar ratio).
- Additional treatment-emergent substitutions in patients treated with bamlanivimab and etesevimab together, with no phenotypic data, include D405del, D420G, C480R, G485D, S494L, and P499L. The impact of these substitutions on susceptibility is not currently known.

It is possible that bamlanivimab and etesevimab resistance-associated variants 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**

Carcinogenesis, mutagenesis, and reproductive toxicology studies with bamlanivimab or etesevimab have not been conducted.

In toxicology studies, bamlanivimab and etesevimab had no adverse effects when administered intravenously to rats and monkeys, respectively. Non-adverse increases in neutrophils were observed in rats dosed with bamlanivimab.

In tissue cross reactivity studies using human adult and fetal tissues, no binding of clinical concern was detected for bamlanivimab or etesevimab.

## **17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA**

#### Antiviral Activity In Vivo

Prophylactic administration of bamlanivimab to female Rhesus macaques (n=3 or 4 per group) resulted in 1 to 4 log<sub>10</sub> decreases in viral genomic RNA and viral replication (sub-genomic RNA) in bronchoalveolar lavage samples relative to control animals, but less of an impact on viral RNA in throat and nasal swabs following SARS-CoV-2 inoculation.

Prophylactic or therapeutic administration of etesevimab to male Rhesus macaques (n=3 per group) resulted in approximately 4 or 3 log<sub>10</sub> average decreases, respectively, in viral genomic RNA in oropharyngeal swabs at Day 4 post infection relative to control animals.

The applicability of these findings to a prophylaxis or treatment setting is not known.

## **18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA**

### **18.1 Treatment of Mild to Moderate COVID-19 (BLAZE-1)**

The data supporting this EUA for treatment of mild to moderate COVID-19 are primarily based on analyses of data from the Phase 2/3 BLAZE-1 trial (NCT04427501). This trial provides Phase 3 placebo-controlled clinical efficacy data from subjects receiving 700 mg bamlanivimab and 1,400 mg of etesevimab together, as well as for subjects receiving 2,800 mg bamlanivimab and 2,800 mg etesevimab together.

BLAZE-1 is a randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). BLAZE-1 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 the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects in the Phase 3 portion of the trial met the criteria for high-risk (as defined in Section 2).

#### Phase 3 Data from BLAZE-1 (bamlanivimab 700 mg and etesevimab 1,400 mg)

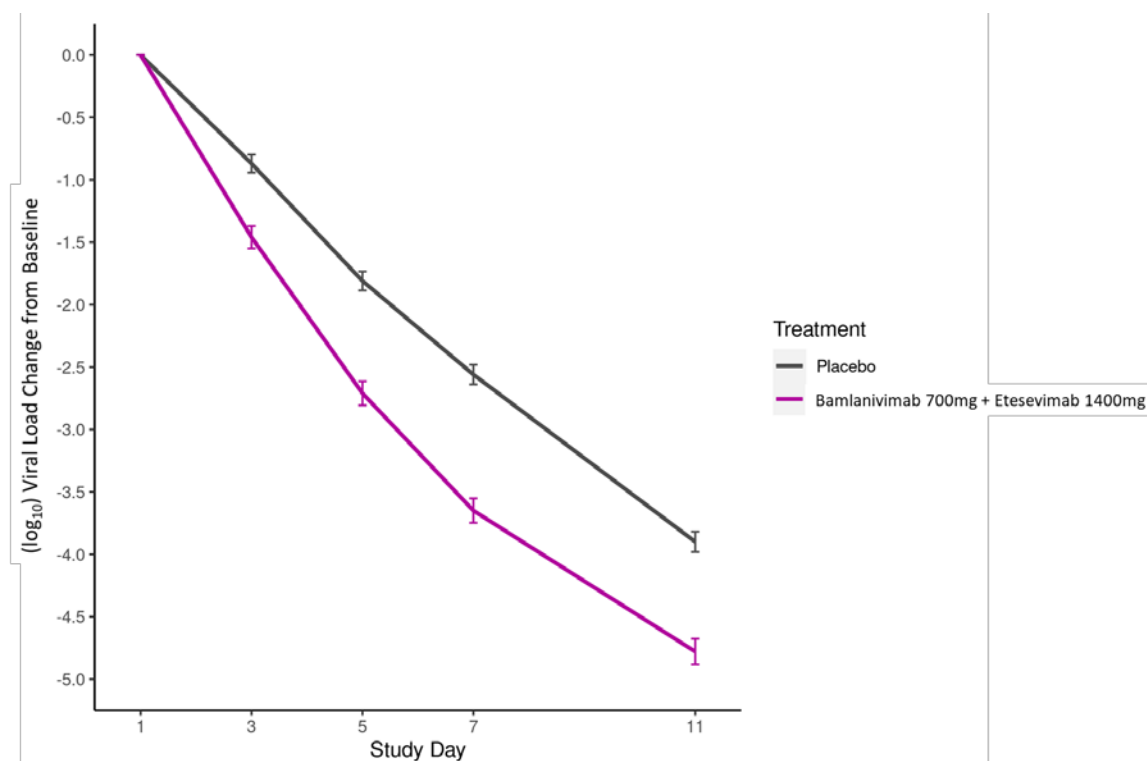
In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg and etesevimab 1,400 mg (N=511) or placebo (N=258). The majority (99.2%) of the patients enrolled in these dose arms met the criteria for high-risk adults (≥18 years of age) that included at least one of the following: age ≥65 years, BMI ≥35, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressant treatment, or age ≥55 years with cardiovascular disease, hypertension, chronic pulmonary disease or other chronic respiratory disease. Participants ages 12-17 were also enrolled in the trial (10 [2.0%] were treated with bamlanivimab and etesevimab and 13 [1.7%] were treated with placebo), and met high-risk criteria as defined in the trial protocol.

At baseline, median age was 56 years (with 30% of subjects aged 65 or older); 53% of subjects were female, 87% were White, 27% were Hispanic or Latino, and 8% were Black or African American. Subjects had mild (76%) to moderate (24%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 24.33 at baseline. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29. Events occurred in 15 subjects treated with placebo (6%) as compared to 4 events in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together (0.8%)

[ $p < 0.0001$ ], an 87% reduction. There were 4 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together ( $p = 0.01$ ).

Secondary endpoints include mean change in viral load from baseline to Day 3, 5, and 7 (Figure 1).



**Figure 1: SARS-CoV-2 Viral Load Change from Baseline (Mean  $\pm$  SE) by Visit from the Phase 3 Portion of BLAZE-1 (700 mg bamlanivimab and 1,400 mg etesevimab).**

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 8 days for subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together as compared with 10 days for subjects treated with placebo ( $p = 0.009$ ). Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Sustained symptom resolution was defined as absence of any of these symptoms, except for allowance of mild fatigue and cough, in two consecutive assessments.

#### Phase 3 Data from BLAZE-1 (bamlanivimab 2,800 mg and etesevimab 2,800 mg)

Subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=518) or placebo (N=517). All of the patients enrolled in these dose arms met the criteria for high-risk adults ( $\geq 18$  years of age) that included at least one of the following: age  $\geq 65$  years of age, BMI  $\geq 35$ , chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressant treatment, or age  $\geq 55$  years with cardiovascular disease, hypertension, chronic pulmonary disease or other chronic respiratory disease. Participants ages 12-17 years were also enrolled in the trial (4 [0.8%]



were treated with bamlanivimab and etesevimab and 7 [1.4%] were treated with placebo), and met high-risk criteria as defined in the trial protocol.

Bamlanivimab 2,800 mg and etesevimab 2,800 mg is not an authorized dosage under this EUA. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as  $\geq 24$  hours of acute care) or death by any cause by Day 29. Events occurred in 36 subjects treated with placebo (7%) as compared to 11 events in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (2%) [ $p < 0.001$ ], a 70% reduction. There were 10 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together ( $p < 0.001$ ).

## **18.2 Post-Exposure Prophylaxis of COVID-19 (BLAZE-2)**

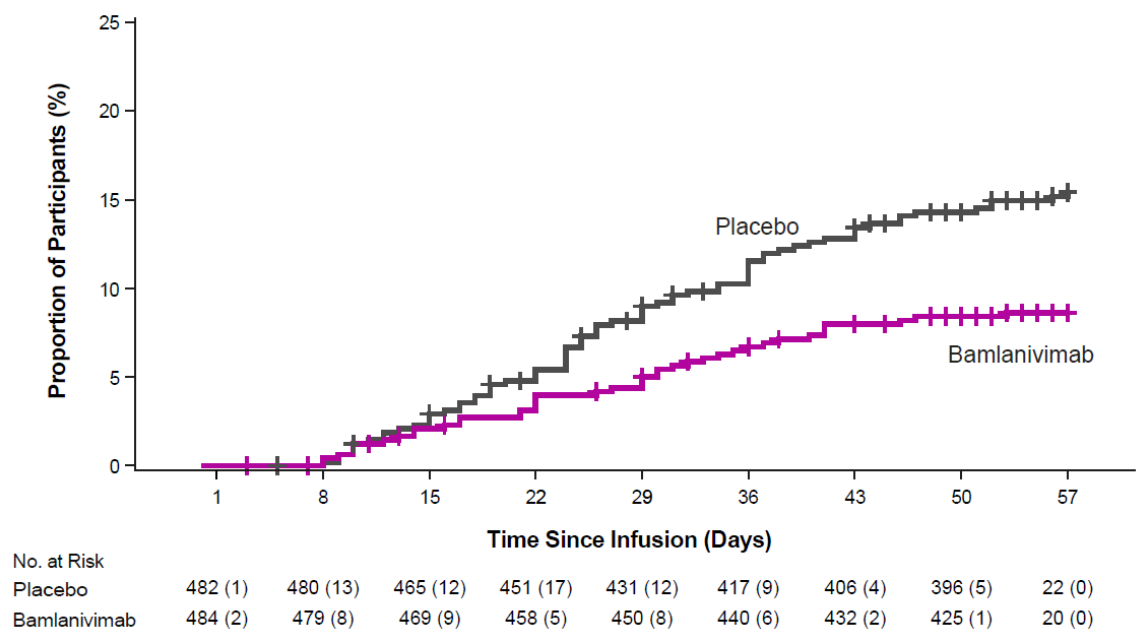
The data supporting this EUA for post-exposure prophylaxis of COVID-19 are based on the final analysis of Part 1 of the Phase 3 trial BLAZE-2 (NCT04497987). The database lock occurred after all enrolled subjects completed Day 57. BLAZE-2 Part 1 is a randomized, double-blind, placebo-controlled study evaluating bamlanivimab alone for prevention of COVID-19 in residents and staff of skilled nursing facilities following a confirmed reported case of SARS-CoV-2 infection at the facility. All participants in Part 1 were randomized and treated with a single infusion of bamlanivimab 4,200 mg or placebo. Results of baseline testing for SARS-CoV-2 were not known until after the therapy was administered. Those with a positive baseline SARS-CoV-2 RT-PCR test were included in the Treatment Population (N=132) and those with a negative test were included in the Prevention Population (N=966). Individuals in these populations were also required to have a baseline negative SARS-CoV-2 serology test; those who tested positive were only included in the overall safety population.

Data are presented for the Prevention Population only. No data were collected on the type or extent of exposure to the index case in the Prevention Population.

In the overall Prevention Population (N=484 for bamlanivimab 4,200 mg and N=482 for placebo) at baseline, the median age was 53 years (with 29% of subjects aged 65 or older); 75% of subjects were female, 89% were White, 5% were Hispanic or Latino, and 8% were Black. The baseline demographics and disease characteristics were well balanced across bamlanivimab and placebo treatment groups.

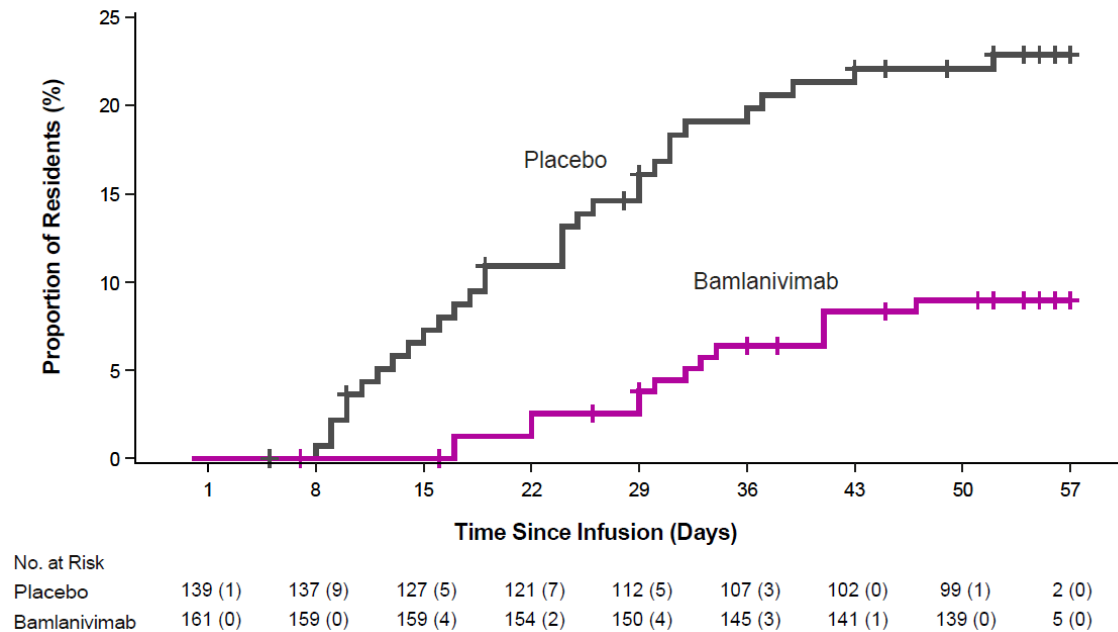
The primary endpoint (cases of symptomatic COVID-19 by Day 57) was assessed after all participants in the Prevention Population reached 8 weeks of follow-up, and analysis were adjusted for facility, sex, and role within facility (resident/staff). There were 114 cases of symptomatic COVID-19, with a lower frequency occurring in participants treated with bamlanivimab as compared to placebo (residents and staff; adjusted odds ratio 0.43;  $p < 0.001$ ) reducing the risk of being infected with COVID-19 by up to 57%. As a supplementary analysis, the time to symptomatic COVID-19 is shown for each arm in

Figure 2. Four COVID-19-related deaths were reported in the overall Prevention Population; all occurred in the placebo arm (0.8%). No COVID-19-related deaths occurred in the bamlanivimab arm.



**Figure 2: Time to symptomatic COVID-19 in the overall prevention population (residents and staff).**

For the pre-specified subgroup of nursing home residents, there were 45 cases of symptomatic COVID-19, with a lower frequency in those treated with bamlanivimab versus placebo (adjusted odds ratio 0.20;  $p<0.001$ ), reducing the risk of being infected with COVID-19 by up to 80%. The time to symptomatic COVID-19 in nursing home residents is shown by treatment arm in Figure 3. In this same cohort of residents within the Prevention Population, 6 deaths due to any cause occurred in residents treated with placebo (4.3%) and 5 deaths due to any cause occurred in residents treated with bamlanivimab (3.1%).



**Figure 3: Time to symptomatic COVID-19 in residents only.**

For the post-hoc subgroup of patients who met the high risk criteria (all residents and all high risk staff<sup>49</sup>), there were 75 cases of symptomatic COVID-19, with a lower frequency in those treated with bamlanivimab versus placebo (adjusted odds ratio 0.28; nominal  $p < 0.001$ ), reducing the risk of being infected with COVID-19 by up to 72%.

For the post-hoc subgroup of staff who did not meet high risk criteria, there were 39 cases of symptomatic COVID-19, with less evidence of a preventative effect for bamlanivimab versus placebo (adjusted odds ratio 0.64; nominal  $p = 0.26$ ).

## 19 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

**UNDER THIS EUA, BAMLANIVIMAB AND ETESEVIMAB MUST BE ADMINISTERED TOGETHER.**

#### Bamlanivimab

Bamlanivimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

#### Etesevimab

Etesevimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

<sup>49</sup> All high risk participants in the Prevention Population were either residents in a skilled nursing or assisted living facility, or staff in a skilled nursing or assisted living facility who satisfied at least 1 of the following at the time of screening: were  $\geq 65$  years of age, had a BMI  $\geq 35$ , had CKD, had diabetes, had immunosuppressive disease, were currently receiving immunosuppressive treatment, OR were  $\geq 55$  years of age AND had cardiovascular disease, OR hypertension, OR COPD or other chronic respiratory disease.

Bamlanivimab and etesevimab are supplied as:

<b>Antibody</b>	<b>Concentration</b>	<b>Package Size</b>	<b>NDC</b>
Bamlanivimab	700 mg/20 mL (35 mg/mL)	one vial per carton	0002-7910-01
Etesevimab	700 mg/20 mL (35 mg/mL)	one vial per carton	0002-7950-01

### **Storage and Handling**

Bamlanivimab is preservative-free. Discard unused portion.

Etesevimab is preservative-free. Discard unused portion.

Store unopened 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, SHAKE, OR 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 infusion solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours and at room temperature (20°C to 25°C [68°F to 77°F]) and for up to 7 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature prior to administration.

## **20 PATIENT COUNSELING INFORMATION**

Patients treated with bamlanivimab and etesevimab 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.LillyAntibody.com](http://www.LillyAntibody.com)

If you have questions, please contact:

1-855-LillyC19 (1-855-545-5921)

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## Appendix 2. Fact Sheet for Patients, Parents and Caregivers

### Fact Sheet for Patients, Parents and Caregivers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab for Coronavirus Disease 2019 (COVID-19)

You are being given two medicines together called **bamlanivimab and etesevimab** for the treatment or post-exposure prophylaxis for prevention of coronavirus disease 2019 (COVID-19). SARS-CoV-2 is the virus that causes COVID-19. This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking bamlanivimab and etesevimab.

Receiving bamlanivimab and etesevimab may help to treat COVID-19 in certain people, or help to prevent COVID-19 in certain people who have been exposed to someone infected with SARS-CoV-2 or who are at high risk of an exposure because of where they live, such as nursing homes or prisons.

Read this Fact Sheet for information about bamlanivimab and etesevimab. Talk to your healthcare provider if you have questions. It is your choice to receive bamlanivimab and etesevimab or stop them at any time.

#### What is COVID-19?

COVID-19 is caused by a virus called a coronavirus, SARS-CoV-2. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, and other conditions including obesity, seem to be at higher risk of being hospitalized for COVID-19. Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.

#### What are the symptoms of COVID-19?

The symptoms of COVID-19 include fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness including breathing problems can occur and may cause your other medical conditions to become worse.

#### What are bamlanivimab and etesevimab?

Bamlanivimab and etesevimab are investigational medicines used together in adults and adolescents (12 years of age and older who weigh at least 88 pounds (40 kg)) who are at high risk for developing severe COVID-19, including hospitalization or death for:

- **treatment** of mild to moderate symptoms of COVID-19, OR
- **post-exposure prophylaxis for prevention** of COVID-19 in persons who are:
  - not fully vaccinated against COVID-19 (Individuals are considered to be fully vaccinated 2 weeks after their second dose in a 2-dose series [such as the Pfizer or Moderna vaccines], or 2 weeks after a single-dose vaccine [such as Johnson & Johnson's Janssen vaccine]), **or**
  - are not expected to build up enough of an immune response to the complete COVID-19 vaccination (for example, someone with immunocompromising conditions, including someone who is taking immunosuppressive medications), **and**
    - have been exposed to someone who is infected with SARS-CoV-2. Close contact with someone who is infected with SARS-CoV-2 is defined as being within 6 feet for a total of 15 minutes or more, providing care at home to someone who is sick, having direct physical contact with the person (hugging or kissing, for example), sharing eating or drinking utensils, or being exposed to respiratory droplets from an infected

- person (sneezing or coughing, for example). For additional details, go to <https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html>, or
- someone who is at high risk of being exposed to someone who is infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons).

Bamlanivimab and etesevimab are investigational because they are still being studied. There is limited information known about the safety or effectiveness of using bamlanivimab and etesevimab to treatment or prevention of COVID-19. Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

The FDA has authorized the emergency use of bamlanivimab and etesevimab together for the treatment of COVID-19 and the post-exposure prophylaxis for prevention of COVID-19 under an Emergency Use Authorization (EUA). For more information on EUA, see the section “**What is an Emergency Use Authorization (EUA)?**” at the end of this Fact Sheet.

### **What should I tell my healthcare provider before I receive bamlanivimab and etesevimab?**

**Tell your healthcare provider about all of your medical conditions, including if you:**

- Have any allergies
- Have received a COVID-19 vaccine
- Have any serious illnesses
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Are taking any medications (prescription, over-the-counter, vitamins, and herbal products)

### **How will I receive bamlanivimab and etesevimab?**

- Bamlanivimab and etesevimab are given to you at the same time through a vein (intravenous or IV).
- You will receive one dose of bamlanivimab and etesevimab by IV infusion. The infusion will take 21 – 60 minutes or longer. Your healthcare provider will determine the duration of your infusion.

### **What are the important possible side effects of bamlanivimab and etesevimab?**

Possible side effects of bamlanivimab and etesevimab are:

- Allergic reactions. Allergic reactions can happen during and after infusion with bamlanivimab and etesevimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low or high blood pressure, rapid or slow heart rate, chest discomfort or pain, weakness, confusion, feeling tired, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, feeling faint, dizziness, and sweating. These reactions may be severe or life threatening.
- Worsening of COVID-19 symptoms after bamlanivimab and etesevimab therapy for active infection: You may experience new or worsening symptoms after infusion for mild to moderate COVID-19, including fever, difficulty breathing, rapid or slow heart rate, tiredness, weakness or confusion. If these occur, contact your healthcare provider or seek immediate medical attention as some of these events have required hospitalization. It is unknown if these events are related to treatment or are due to the progression of COVID-19.

The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

These are not all the possible side effects of bamlanivimab and etesevimab. Not a lot of people have been given bamlanivimab and etesevimab. Serious and unexpected side effects may happen. Bamlanivimab and etesevimab are still being studied so it is possible that all of the risks are not known at this time.

It is possible that bamlanivimab and etesevimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, bamlanivimab and etesevimab may reduce your body's immune response

to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

#### **What other treatment choices are there?**

Like bamlanivimab and etesevimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization> for information on the emergency use of other medicines that are not approved by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials you may be eligible for.

It is your choice to be treated or not to be treated with bamlanivimab and etesevimab. Should you decide not to receive bamlanivimab and etesevimab or stop it at any time, it will not change your standard medical care.

#### **What other prevention choices are there?**

Vaccines to prevent COVID-19 are approved or available under Emergency Use Authorization. Use of bamlanivimab and etesevimab does not replace vaccination against COVID-19.

Like bamlanivimab and etesevimab, FDA may allow for the emergency use of other medicines for post-exposure prophylaxis for prevention of COVID-19. Go to <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization> for information on the emergency use of other medicines that are not approved by FDA for post-exposure prophylaxis for prevention of COVID-19. Your healthcare provider may talk with you about clinical trials you may be eligible for.

Bamlanivimab and etesevimab are not authorized for pre-exposure prophylaxis for prevention of COVID-19.

#### **What if I am pregnant or breastfeeding?**

There is limited experience treating pregnant women or breastfeeding mothers with bamlanivimab and etesevimab. For a mother and unborn baby, the benefit of receiving bamlanivimab and etesevimab may be greater than the risk from the treatment. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

#### **How do I report side effects with bamlanivimab and etesevimab?**

Tell your healthcare provider right away if you have any side effect that bothers you or does not go away.

Report side effects to **FDA MedWatch** at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), call 1-800-FDA-1088, or contact Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921).

#### **How can I learn more?**

- Ask your healthcare provider
- Visit [www.LillyAntibody.com](http://www.LillyAntibody.com)
- Visit <https://www.covid19treatmentguidelines.nih.gov/>
- Contact your local or state public health department

#### **What is an Emergency Use Authorization (EUA)?**

The United States FDA has made bamlanivimab and etesevimab available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

Bamlanivimab and etesevimab have not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA must determine, among other things, that based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are

no adequate, approved and available alternatives. All of these criteria must be met to allow for the medicine to be used in the treatment of COVID-19 or prevention of COVID-19 during the COVID-19 pandemic.

The EUA for bamlanivimab and etesevimab together is in effect for the duration of the COVID-19 declaration justifying emergency use of these products, unless terminated or revoked (after which the products may no longer be used).

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WENDY W CARTER  
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DEBRA B BIRNKRANT  
09/15/2021 05:15:04 PM

JOHN J FARLEY  
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**CLINICAL REVIEW**  
**US FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**OFFICE OF INFECTIOUS DISEASES**  
**DIVISION OF ANTIVIRALS**  
**ADDENDUM**

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<b>EUA:</b>	000094
<b>Product:</b>	Bamlanivimab and etesevimab
<b>Sponsor:</b>	Eli Lilly and Company
<b>Intended Population:</b>	Adults and pediatric patients (12 years of age and older and weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death

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This addendum references the summary EUA review for bamlanivimab and etesevimab, dated September 16, 2021 that added the authorized use for post-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19.

On page 51 of the summary EUA review Section XIII, Nonclinical Data to Support Efficacy, the fold-reduction in susceptibility of Q493R substitution to bamlanivimab and etesevimab together is shown as >100-fold; this is corrected to 1,054-fold.

On page 52, the fold-reduction in susceptibility of K417T + E484K + N501Y substitutions found in the P.1 lineage to bamlanivimab and etesevimab together is shown as >511-fold; this this is corrected to >3,351-fold.

On page 61 of the summary EUA review Section XX, Risk-Benefit Assessment and Recommendations for Emergency Use, it should state that “the authorized use language in the Fact Sheet includes examples of these conditions and cites the CDC’s website as a resource to guide the treating physicians who are considering the use of **bamlanivimab and etesevimab** prophylaxis in an individual expected to develop inadequate response to complete SARS-CoV-2 vaccination.”

These corrections replace the errors made in the September 16, 2021 summary EUA review. These corrections do not alter the conclusion of the review or alter the information presented in the authorized Facts Sheets for Healthcare Providers or for Patients, Parents and Caregivers.

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/s/  
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NATALIE M PICA  
10/04/2021 05:16:27 PM

WENDY W CARTER  
10/04/2021 05:17:06 PM

DEBRA B BIRNKRANT  
10/04/2021 06:02:51 PM

JOHN J FARLEY  
10/04/2021 06:34:54 PM