**Emergency Use Authorization (EUA) for**
**Bamlanivimab 700 mg and Etesevimab 1400 mg IV Administered Together**
**Center for Drug Evaluation and Research (CDER) Review**

## Identifying Information

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| Application Type (EUA or Pre-EUA)<br>If EUA, designate whether pre-event or intra-event EUA request. | EUA |
| EUA Application Number(s)[1] | EUA 000094 |
| Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address | Eli Lilly and Company<br>Christine Phillips, PhD, RAC<br>Advisor, Global Regulatory Affairs - NA<br>Mobile: (b) (6)<br>Email: phillips_christine_ann@lilly.com |
| Manufacturer, if different from Sponsor | Eli Lilly and Company |
| Submission Date(s) | November 16, 2020 |
| Receipt Date(s) | November 16, 2020 |
| OND Division / Office | Division of Antivirals/Office of Infectious Diseases |
| Reviewer Name(s)/Discipline(s) | Natalie Pica, MD, PhD – Clinical Reviewer<br>Wendy Carter, DO – Cross Discipline Team Lead<br>Michael Thomson, PhD – Clinical Virology Reviewer<br>Jules O'Rear, PhD – Clinical Virology Team Lead<br>Daniel Rubin, PhD – Statistics Reviewer<br>Thamban Valappil, PhD – Statistics Team Lead<br>Dionne Price, PhD – Director, Division of Biometrics IV<br>Jason Moore, PharmD – Clinical Pharmacology Reviewer<br>Su-Young Choi PharmD, PhD – Clinical Pharmacology Team Lead<br>Kellie Reynolds, PharmD – Division Director, DIDP<br>Ye Xiong, PhD – Pharmacometrics Reviewer<br>Justin Earp, PhD – Pharmacometrics Team Lead<br>Yaning Wang, PhD – Division Director, DPM |

[1] If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

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| Integrated Review Completion Date | |
| 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<br>Etesevimab - 1400mg IV |
| Therapeutic Class | SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibodies (mAbs) |
| Intended Use or Need for EUA | Mild to moderate COVID-19 |
| Intended Population(s) | 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 illness and/or hospitalization |
| 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 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 is now 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

The Division of Antivirals, Office of Infectious Diseases, Office of New Drugs, CDER recommends EUA issuance.

The EUA will authorize 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 progressing to severe COVID-19 and/or hospitalization.

### B. 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.
- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective 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 progressing to severe COVID-19 and/or hospitalization, and when used under such conditions, the known and potential benefits of bamlanivimab and etesevimab 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 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 progressing to severe COVID-19 and/or hospitalization. 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. Remdesivir (Veklury®) is the only drug that is approved by FDA to treat COVID-19 at the time of FDA's review of bamlanivimab and etesevimab. Remdesivir is a nucleoside ribonucleic acid polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir's approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization.

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

Proposed Use Under EUA:

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 progressing to severe COVID-19 and/or hospitalization.

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
    - cardiovascular disease, OR
    - hypertension, OR
    - chronic obstructive pulmonary disease/other chronic respiratory disease
- Are 12 – 17 years of age AND have
    - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
    - sickle cell disease, OR
    - congenital or acquired heart disease, OR
    - neurodevelopmental disorders, for example, cerebral palsy, OR
    - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
    - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

**LIMITATIONS OF AUTHORIZED USE**

- 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.

Authorized Dosage Under EUA:

*Adults and Pediatric Patients:*

The authorized dosage for bamlanivimab and etesevimab for adults and pediatric patients (12 years of age and older weighing ≥40 kg) is a single intravenous (IV) infusion of 700 mg bamlanivimab and 1400 mg etesevimab administered together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

*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 (18 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 XI for more details.

*Rationale for Dose:*
The dosage of 700 mg bamlanivimab and 1,400 mg etesevimab administered together was selected based on analyses of available data incorporating the following factors:

- Available data demonstrate that a dosage of 700 mg bamlanivimab and 1,400 mg etesevimab administered together has similar antiviral activity to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab administered together. Refer to Section VIII and XI for further details.
- A dosage of 700 mg bamlanivimab and 1,400 mg etesevimab is expected to provide near-maximal antiviral activity based on in vitro data and pharmacokinetics/pharmacodynamics (PK/PD) modeling of clinical data. This dosage of bamlanivimab and etesevimab is estimated to achieve serum concentrations above their respective in vivo $EC_{90}$ values for at least 28 days. Refer to sections XIII and XI for further details on the determination of the in vivo $EC_{90}$ values.
- A dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab administered together, reduced COVID-19 related hospitalizations and deaths in addition to significantly reducing viral load relative to placebo in a randomized, double-blinded, placebo-controlled trial conducted by Eli Lilly (Trial J2W-MC-PYAB, BLAZE-1, NCT04427501).
- Bamlanivimab and etesevimab administered together resulted in fewer treatment-emergent variants relative to bamlanivimab alone.

Based on analyses of the available nonclinical, clinical, and virologic data, as well as supportive data from pharmacokinetic/pharmacodynamic modeling, the authorized dosage of 700 mg bamlanivimab and 1,400 mg etesevimab is expected to have similar clinical effect to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab.

## IV. Product Information (Dose Preparation and Administration)
## 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 pre-filled 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 pre-filled 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[a] in Patients Weighing 50 kg or More**

| **Drug[a]: 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 |

[a] 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[a]: 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[b] | 266 mL/hr | 70 minutes |

[a] 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.
[b] 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).

During the conduct of Trial PYAB, patients received 2800 mg of bamlanivimab and 2800 mg of etesevimab over an hour, resulting in the administration of 93 mg of protein per minute. With this authorization, 700 mg bamlanivimab and 1,400 mg etesevimab can be administered together over 21 to 60 minutes (see and Table 2 above), resulting in a delivery of 30mg to 100 mg of protein per minute.

Data and information were provided to support that 60 mL of product (20 mL of bamlanivimab and 40 mL of etesevimab) can be accommodated by pre-filled 0.9% sodium chloride infusion bags of various sizes and from various commonly used vendors. Simulated in-use compatibility and stability studies were also performed.

Because bamlanivimab and etesevimab are to be used together and are packaged separately under the EUA authorization, a Dear Health Care Provider letter is included under the authorization to outline the differences between use of bamlanivimab alone and bamlanivimab and etesevimab administered together in an effort to minimize the risk of medication errors.

**How Supplied/Storage and Handling**

**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:

| Antibody | Concentration | Package Size | NDC |
|---|---|---|---|
| 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

There are many types of human coronaviruses including some that commonly cause mild upper-respiratory tract illness. 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 105 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported globally as of February 7, 2021, including an estimated 2.3 million deaths. In the US, according to the Center for Disease Control and Prevention (CDC) as of February 7, 2021, approximately 26,761,047 cases of COVID-19 have been reported with an associated 460,582 deaths.

Per the CDC, COVID-19 reported in the United States has disproportionally affected the elderly. While approximately 14% of those infected with COVID-19 have been 65 years of age or older, this has accounted for approximately 81% of total deaths (https://covid.cdc.gov/covid-data-tracker/#demographics accessed on 1/24/2021). These findings are similar to data from China, which indicated >80% of deaths occurred among persons aged ≥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

(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).

Therapeutic Alternatives for the Disease

There is no adequate, approved, and available alternative to the emergency use of bamlanivimab and etesevimab for the treatment of mild to moderate 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.

There is an approved drug and other EUAs authorized for other COVID-19 treatments. Remdesivir (Veklury®) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor approved for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. This medication was initially authorized for emergency use on May 1, 2020 and was ultimately approved for the treatment of adults and certain pediatric patients with COVID-19 requiring hospitalization on October 22, 2020 under NDA 214787.[2]

Baricitinib, an inhibitor of janus kinase, has been authorized for emergency use in combination with remdesivir for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplementary oxygen, invasive mechanical ventilation, or extra-corporeal membrane oxygenation (ECMO).

Bamlanivimab 700 mg was authorized for emergency use on November 9, 2020 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 progressing to severe COVID-19 and/or hospitalization.

Other monoclonal antibodies have been authorized for emergency use for patients with mild to moderate COVID-19 as well. On November 21, 2020, casirivimab 1200 mg and imdevimab 1200 mg were authorized to be 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 progressing to severe COVID-19 and/or hospitalization.

[2] At the time of this review, remdesivir remains authorized for emergency use for treating suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

There are currently no approved therapies for treatment of COVID-19 in non-hospitalized patients.

Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html.

## VI. Related Regulatory Submission(s)

Bamlanivimab and etesevimab have been studied under INDs 150440, 150707, 151193, 151543, and 153935 (Table 3). Bamlanivimab 700 mg administered alone is authorized under Emergency Use Authorization (EUA 90).

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 etesevimab:

- DMF 21219
  - Procedure for Sterile Operations in Building B103, Indianapolis, IN
  - Holder: Eli Lilly & Company
- 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)

## VII. Summary of Clinical Data

The data to support the authorization of bamlanivimab and etesevimab administered together were generated from phase 1, phase 2, and phase 3 clinical trials (Table 3).

The initial EUA request for the use of bamlanivimab and etesevimab administered together 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 illness and/or hospitalization, was received on November 16, 2020. At that time, the principle efficacy and safety data were from Treatment Arms 1-4 and 6 of Trial PYAB (BLAZE-1) and therefore, the majority of the review focuses on these data. The study population in Treatment

Arms 1-4 and 6 included subjects with mild or moderate COVID-19 symptoms, with and without risk factors for severe disease progression and/or hospitalization.

While the EUA request was reviewed following its receipt, the Applicant submitted topline results for Treatment Arms 7 and 8 of Trial PYAB on January 25, 2021. These arms, which serve as the phase 3 portion of the trial, enrolled subjects with mild to moderate COVID-19 who also had risk factors for progression to severe COVID-19 illness and/or hospitalization. The topline efficacy and safety data are reviewed in this document.

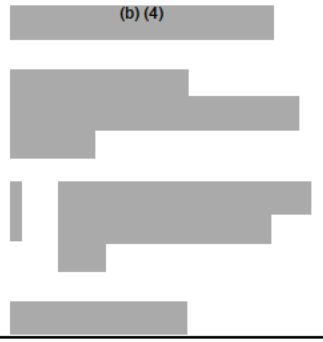
On January 31, 2021, the Applicant submitted topline data from Trial PYAH, a clinical trial that evaluates safety and efficacy of bamlanivimab alone and bamlanivimab and etesevimab administered together in non-hospitalized subjects with mild or moderate COVID-19 illness. The data from Trial PYAH strengthened the bridge between bamlanivimab 2800 mg and etesevimab 2800 mg and the authorized dose of bamlanivimab 700 mg and etesevimab 1400 mg. These data were considered supportive of this authorization and are included in the clinical efficacy and safety sections of this review document.

**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<br><br>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<br>Cohorts 1- 3:<br>6 received BAM, 2 received placebo<br>• Cohort 1 = 700 mg BAM<br>• Cohort 2 = 2800 mg BAM<br>• Cohort 3 = 7000 mg BAM<br><br>Assessments to Day 29; 60-day follow-up | Completed<br><br>Enrollment N = 26<br>Cohort 1: N = 8<br>Cohort 2: N = 9<br>Cohort 3: N = 9<br><br>Clinical Study Report approved 19 November 2020 |
| J2W-MC-PYAB (BLAZE-1) | 150440 | Efficacy, Safety | N = 3890<br><br>**Phase 2**<br>Mild to moderate COVID-19<br><br>Treatment Arms 1-4 & 6: N = 500 participants plus additional placebo to ensure up to 50 concurrent placebo controls for treatment Arm 6<br><br>**Phase 3**<br>Mild to moderate COVID-19 with at least 1 risk factor for developing severe COVID-19 illness; includes adults and adolescents<br><br>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<br><br>Addendum 2 (Arm 15): open label, substudy to evaluate safety and efficacy of BAM and ETE in patients 0 to ≤17 years. Dose of BAM and ETE are adjusted by patient weight to match exposures of (b) (4) BAM and (b) (4) ETE in adults, based on PK/PD modeling | Single IV infusion in Treatment Arms 1-18; single subcutaneous administration in Arm 19<br><br>**Phase 2:**<br>• Arm 1: Placebo, ~100 concurrent with Arms 2 and 3; 50 concurrent with Arm 6<br>• Arm 2: 700 mg BAM<br>• Arm 3: 2800 mg BAM<br>• Arm 4: 7000 mg BAM<br>• Arm 6: 2800 mg BAM + 2800 mg ETE<br><br>**Phase 3:**<br>• Arm 7: 2800 mg BAM + 2800 mg ETE<br>• Arm 8: Placebo, concurrent with Arms 7 and 9 | (b) (4)<br><br>Enrollment N = 2657<br><br>**Phase 2:**<br>N = 592[a]; 577 received trial medication<br>Arm 1: N = 156<br>Arm 2: N = 101<br>Arm 3: N = 107<br>Arm 4: N = 101<br>Arm 6: N = 112<br><br>**Phase 3:**<br>(Arm 8 in parallel with Arm 7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | Treatment Arms 9: N = ~ 500 participants<br><br>Treatment Arms 13 and 14: N = 160 for placebo, N = 240 for BAM + ETE<br><br>Treatment Arm 15: N = ~50 participants ages 0 to ≤17 years using weight-based dosing<br><br>Treatment Arm 16 and 17: N = ~220 participants; these arms investigate faster infusion times<br><br>Treatment Arm 18: N = ~460 participants<br><br>Treatment Arm 19: N = ~460 participants | | • Arm 9: 700 mg BAM + 1400 mg ETE<br>• Arm 13: Placebo<br>• Arm 14: (b) (4) BAM + ETE (b) (4)<br>• Arm 15: BAM + ETE using weight-based dosing<br>• Arm 16: (b) (4) BAM + (b) (4) ETE<br>• Arm 17: (b) (4) BAM + (b) (4) ETE<br>• Arm 18: 700 mg BAM + 1400 mg ETE<br>• Arm 19: (b) (4) BAM + (b) (4) ETE<br><br>Assessments to Day 29; 85-day follow-up | N = 1035<br>Arm 7: 518<br>Arm 8: 517<br><br>(Arm 8 in parallel with Arm 9 (b) (4)<br>Arm 8: Blinded<br>Arm 9: Blinded<br><br>Arms 13 and 14 (b) (4)<br>Arm 13: Blinded<br>Arm 14: Blinded<br><br>(b) (4) |
| J2X-MC-PYAD (BLAZE-2) | 150440 | Efficacy, Safety | N = ≤5000 (maximum sample size) Residents and staff of skilled nursing or assisted living facilities; Prevention and treatment cohorts<br><br>**Part 1** will randomize up to 1700 participants<br><br>**Part 2** will randomize up to 2000 participants<br><br>**Part 3** will randomize up to 500 participants. The maximum sample size for this trial is approximately 5000 participants in the ITT population. | Phase 3, randomized, double-blind, placebo-controlled study<br><br>**Part 1**: goal of achieving ~33 events (in each of the primary and key secondary endpoints) in the prevention population<br><br>**Part 2**: goal of achieving ~56 events on each of the primary and key secondary endpoints in the Prevention Cohort | Single IV infusion<br><br>**Part 1:**<br>• Arm 1: 4200 mg BAM<br>• Arm 2: Placebo<br><br>**Part 2:**<br><u>Prevention Cohort</u><br>• Arm 3: 700 mg BAM<br>• Arm 4: (b) (4) BAM + (b) (4) ETE<br>• Arm 5: Placebo<br><br>Evaluation period of 8 weeks; 169-day follow-up | Part 1, active, not enrolling<br><br>Enrollment<br>**Part 1:**<br>N = 1299 observed<br>Arm 1: 588<br>Arm 2:587<br><br>**Part 2:**<br>Not yet enrolling<br><br>**Part 3:**<br>(b) (4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | **Part 3:** considered exploratory and is not powered for inference between the two treatment arms | <u>Treatment Cohort:</u><br>• Arm 6: 700 mg BAM<br>• Arm 7: 2800 mg BAM + 2800 mg ETE<br><br>Evaluation period of 8 weeks; 85-day follow-up<br><br>**Part 3:**<br>• Arm 8: 700 mg BAM<br>• Arm 9: 700 mg BAM + 1400 mg ETE<br><br>Evaluation period of 4 weeks; 85-day follow-up | |
| J2X-MC-PYAG | 150440 | PK, Safety | N = 27<br>Healthy volunteers | Phase 1, randomized, placebo-controlled, participant- and investigator- blind, SC, PK trial | Single SC administration<br><br>Cohorts 1- 3:<br>7 received BAM, 2 received placebo<br>• Cohort 1 = (b) (4) BAM<br>• Cohort 2 = 700 mg BAM<br>• Cohort 3 = (b) (4) BAM<br><br>12-week follow-up | Active, closed to enrollment<br><br>Enrollment<br>N = 25<br><br>Cohort 1: N = 9<br>Cohort 2: N = 9<br>Cohort 3: N = 7 |
| J2X-MC-PYAH (BLAZE-4) | 150440 | Efficacy, Safety | N = ~1100<br>Mild to moderate COVID-19<br><br>Substudy 1<br>N = 66<br><br>Substudy 2<br>N = 212 | Phase 2, placebo-controlled, double-blind, randomized, single-dose trial in participants with mild-to-moderate COVID-19 illness<br><br>Substudy 1: Open-label substudy to explore accelerated IV administration of BAM alone, and with ETE<br><br>Sub-study 2: Open-label substudy to explore | Single IV infusion<br><br>• Arm 1: Placebo<br>• Arm 2: (b) (4) BAM + (b) (4) ETE<br>• Arm 3: 700 mg BAM + 1400 mg ETE<br>• Arm 4: 2800 mg BAM + 2800 mg ETE<br>• Arm 5: 700 mg BAM<br>• Arm 6: (b) (4) BAM + (b) (4) ETE<br>• Arm 7: 700 mg BAM + 500 mg VIR-7831<br>• Arm 8: Placebo | Active, Arms 1-6: Enrollment complete.<br>(b) (4)<br><br>Enrollment<br>N = 731 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | treatment administration of 15 minutes of less with BAM alone, and with ETE | **Substudy 1:**<br>• Arm A: 700 mg BAM<br>• Arm B: 700 mg BAM + 1400 mg ETE<br><br>**Substudy 2:**<br>• Arm C: 700 mg BAM<br>• Arm D: (b) (4) BAM + (b) (4) ETE | Arms 1-6: Blinded<br>  |
| J2Z-MC-PGAA | 150707 | PK, safety | N = ≤ 30<br>Healthy volunteers | Phase 1, randomized, placebo-controlled trial |  | Completed<br><br>Enrollment<br>N = 26<br><br>Cohort 1: N = 9<br>Cohort 2: N = 9<br>Cohort 3: N = 8<br><br>Clinical Study Report approved 02 December 2020 |
| J2Z-MC-PGAB | 150707 | PK, safety | N = ≤ 22<br>Healthy volunteers | Phase 1, randomized, placebo-controlled trial |  | Active, enrolling<br><br>Enrollment<br>N = 18<br><br>Cohort 1: N = 9<br>Cohort 2: N = 9 |

| | | | | | | |
|---|---|---|---|---|---|---|
| J2X-MC-PYAJ (BLAZE-5) | 150440 | Efficacy, safety | Study Participants:<br>N = 3000 adults and children (≥12 years) infected with SARS-CoV-2, at high risk of developing severe disease requiring hospitalization<br><br>Matched Controls:<br>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<br><br>Follow-up on Days 2, 29, 60, 90 | Active, enrolling<br>(b) (4) |
| JS016-001-I | NA[b] | PK, safety | N = 40<br>Healthy Chinese volunteers | Phase 1, randomized, double-blind, placebo-controlled trial | (b) (4) | Active, closed to enrollment (DBL = 04 November 2020)<br><br>Enrollment<br>N = 40 |
| ACTIV-2 | 151193 | Efficacy, safety | N = 220 for phase 2<br>N = 1000 per arm for phase 3, inclusive of the patients enrolled in the phase 2 portion of the trial<br><br>Outpatient adults positive for SARS-CoV-2 | Phase 2/3, randomized, blinded, controlled, platform trial | Single IV infusion<br><br>**Phase 2**:<br>• Arm 1: Placebo<br>• Arm 2: 7000 mg BAM initially, dose then changed to 700 mg BAM<br><br>**Phase 3:**<br>• Arm 1: Placebo<br>• Arm 2: 700 mg BAM | Ongoing<br><br>Enrollment<br>N = 1295<br><br>**Phase 2:**<br>Arm 1: Blinded<br>Arm 2:<br>N = 97 (7000 mg)<br>N = 222 (700 mg)<br><br>**Phase 3:** |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 28 days of intensive follow-up, followed by limited follow-up through 24 weeks | Open Label<br>Arm 2:<br>N = 976 (700 mg) |
| ACTIV-3 | 151543 | Efficacy, Safety | N = 1000<br>**Stage 1**<br>N= 150 participants per IA/placebo: Inpatient adults with COVID-19 symptoms, without end organ failure<br><br>**Stage 2**<br>N = 500 participants per IA/ placebo (including those from Stage 1) | Phase 3, randomized, blinded, controlled platform study with 2 stages | Single IV infusion<br><br>**Stage 1:**<br>• Arm 1: Placebo<br>• Arm 2: 7000 mg BAM<br><br>Follow-up 90 days | Ongoing, but accrual of patients receiving bamlanivimab stopped due to lack of benefit per the DSMB meeting on 26 October 2020<br><br>Enrollment<br>N = 326<br>**Stage 1:**<br>Arm 1: Blinded<br>Arm 2: Blinded<br><br>**Stage 2:**<br>Not enrolling |
| 2020-0081 | 153935<br>Sponsored by SavvySherpa, LLD d/b/a Optum Labs | Efficacy, Safety | Study participants:<br>N = 7500<br>UHC members (≥65 years) deemed at high risk of contracting COVID-19<br><br>Matched controls:<br>N = 7500<br>UHC members (≥65 years) that seek care at an Optum Care facility for confirmed symptomatic COVID-19 | Open label, single-arm, pragmatic, observational study using matched, real-world external controls (no placebo arm)<br><br>Infusions to be administered at home by an Optum Infusion Nurse | Study participants will receive 700 mg BAM<br>Follow-up 18 days; up to 6 months of symptom tracking post-infusion<br><br>Match on controls will be followed for up to 38 after symptom onset | Active<br><br>(b) (4) |

[a] 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.
[b] Not applicable. Trial sponsored by Junshi Biosciences in China and not under a US IND.
[c] Non-UHC members may be used as members of the control population based on electronic medical record review and matching to enrolled participants
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; 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.
Source: Adapted from Applicant Submission to EUA dated February 4, 2021entitled “Updated Table of Clinical Studies”

## VIII. Clinical Efficacy

The main source of clinical efficacy data submitted with the EUA request was from a planned phase 2 interim analysis of Trial PYAB (also called BLAZE-1). However, subsequently on January 25, 2021, the Applicant submitted topline efficacy data from the phase 3 portion of the ongoing PYAB trial. These data showed a significant clinical benefit of reduction in hospitalization and all-cause mortality by Day 29 for bamlanivimab 2800 mg and etesevimab 2800 mg administered together compared to placebo in outpatients at high risk of progression to severe COVID-19. On January 31, 2021, the Applicant submitted additional topline virologic results from the phase 2 Trial PYAH (also called BLAZE-4) that was intended to inform dosing. This section of the review first presents the phase 2 data from Treatment Arms 1-4 and 6 of PYAB in detail as this was the basis of the initial EUA request, and then provides a discussion of the phase 3 Treatment Arms 7 and 8 topline data submitted on January 25, 2021. This section then briefly discusses virologic results from Trial PYAH followed by an analysis of spike protein variants.

Overview of Trial PYAB (BLAZE-1)

Trial PYAB (clinicaltrials.gov identifier NCT04427501) is an ongoing, randomized, double-blind, placebo-controlled, phase 2/3 trial of bamlanivimab alone and bamlanivimab and etesevimab administered together in outpatients with mild to moderate COVID-19. The treatment arms and enrolled populations in Trial PYAB used in the efficacy assessments in this review are shown in the table below.

**Table 4: Treatment Arms in Trial PYAB Assessed in This Review**

| Arm | Treatment and dose | Population | Sample size | Enrollment status |
|---|---|---|---|---|
| 1 | Placebo | Outpatients | 156 | Complete |
| 2 | Bamlanivimab 700 mg | Outpatients | 101 | Complete |
| 3 | Bamlanivimab 2800 mg | Outpatients | 107 | Complete |
| 4 | Bamlanivimab 7000 mg | Outpatients | 101 | Complete |
| 5 | Optional arm never entered into the trial | N/A | 0 | Never enrolled |
| 6 | Bamlanivimab 2800 mg and etesevimab 2800 mg | Outpatients | 112 | Complete |
| 7 | Bamlanivimab 2800 mg and etesevimab 2800 mg | High risk outpatients | 518 | Complete |
| 8 | Placebo | High risk outpatients | 517 | Complete |

Source: EUA Request and IND 150440 SDN 111.

The trial began by randomizing participants to a single dose of placebo (Treatment Arm 1) versus bamlanivimab 700 mg (Treatment Arm 2). The higher bamlanivimab monotherapy doses of 2800 mg (Treatment Arm 3) and 7000 mg (Treatment Arm 4) were sequentially entered into the trial

after being found safe in the separate phase 1 study, Trial PYAA. Treatment Arm 5 was an optional group that was never entered into the study. The bamlanivimab 2800 mg and etesevimab 2800 mg group (Treatment Arm 6) was subsequently entered. Results for Treatment Arms 1-4 and 6 will first be discussed together because these constituted phase 2 data intended for dose finding and initial efficacy assessments.

The trial next randomized over 1000 participants at high risk for progression to severe COVID-19 disease to bamlanivimab 2800 mg and etesevimab 2800 mg (Treatment Arm 7) versus placebo (Treatment Arm 8). Topline results of this interim analysis were submitted on January 25, 2021. This larger concurrently randomized comparison was intended to provide standalone evidence of safety and efficacy to support an eventual Biological License Application.

Randomization is still ongoing for additional treatment arms, including evaluation of bamlanivimab 700 mg and etesevimab 1400 mg compared to placebo (Treatment Arms 8 and 9), in patients with mild to moderate COVID-19 who are at high risk for progression to more severe COVID-19 disease. Unblinded comparative results are not yet available for these additional groups that are intended to refine dosing.

This review will first discuss the phase 2 data from Treatment Arms 1-4 and 6 and then separately discuss the topline results from Treatment Arms 7-8.

Efficacy Results for Trial PYAB Treatment Arms 1-4 and 6 (Phase 2)

Inclusion criteria for enrollment in Trial PYAB Treatment Arms 1-4 and 6 specified that participants were not hospitalized at the time of enrollment, had 1 or more mild or moderate COVID-19 symptoms, and had sample collection for the first positive SARS-CoV-2 viral infection determination ≤3 days prior to the start of the infusion.

The table below displays demographic and baseline characteristics. Slightly over half of participants were female. Approximately 40% of participants were Hispanic or Latino while under 10% in all groups were Black or African American. On average, participants had been symptomatic for approximately 5 days before the baseline visit. Approximately 10% of participants were seropositive for the SARS-CoV-2 virus at baseline as determined by the Elecsys Anti-SARS-CoV-2 assay. The placebo group had a higher proportion of patients (44%) at high risk of hospitalization than the bamlanivimab and etesevimab group (34%).

**Table 5: Baseline Demographics and Disease Characteristics in Trial PYAB (Treatment Arms 1-4 and 6)**

| | Placebo (N = 156) | BAM 700 mg (N = 101) | BAM 2800 mg (N = 107) | BAM 7000 mg (N = 101) | BAM 2800 mg and ETE 2800 mg (N = 112) |
|---|---|---|---|---|---|
| Female | 85 (54%) | 63 (62%) | 51 (48%) | 58 (57%) | 58 (52%) |
| Hispanic or Latino | 68 (44%) | 49 (49%) | 47 (44%) | 39 (39%) | 42 (38%) |
| Black or African American | 7 (5%) | 7 (7%) | 7 (7%) | 8 (8%) | 4 (4%) |
| Age (median years) | 46 | 39 | 45 | 46 | 44 |
| Age ≥ 65 years | 23 (15%) | 11 (11%) | 8 (7%) | 14 (14%) | 13 (12%) |
| BMI (mean $kg/m^2$) | 30 | 31 | 30 | 29 | 29 |
| 30 ≤ BMI < 40 | 63 (41%) | 34 (34%) | 50 (47%) | 28 (30%) | 33 (30%) |
| BMI ≥ 40 | 9 (6%) | 11 (11%) | 6 (6%) | 7 (7%) | 7 (6%) |
| High risk of hospitalization | 68 (44%) | 46 (46%) | 46 (43%) | 44 (44%) | 38 (34%) |
| Mild COVID-19 | 124 (79%) | 83 (82%) | 79 (74%) | 70 (69%) | 92 (82%) |
| Moderate COVID-19 | 32 (20%) | 18 (18%) | 28 (26%) | 31 (31%) | 20 (18%) |
| Duration of symptoms (days, mean) | 5 | 5 | 5 | 5 | 5 |
| Duration of symptoms ≤ 10 days | 149 (96%) | 96 (95%) | 103 (96%) | 97 (96%) | 110 (98%) |
| Viral load (mean, CT value) | 24 | 24 | 25 | 24 | 23 |
| Seropositive | 12 (8%) | 10 (10%) | 15 (14%) | 14 (14%) | 12 (11%) |

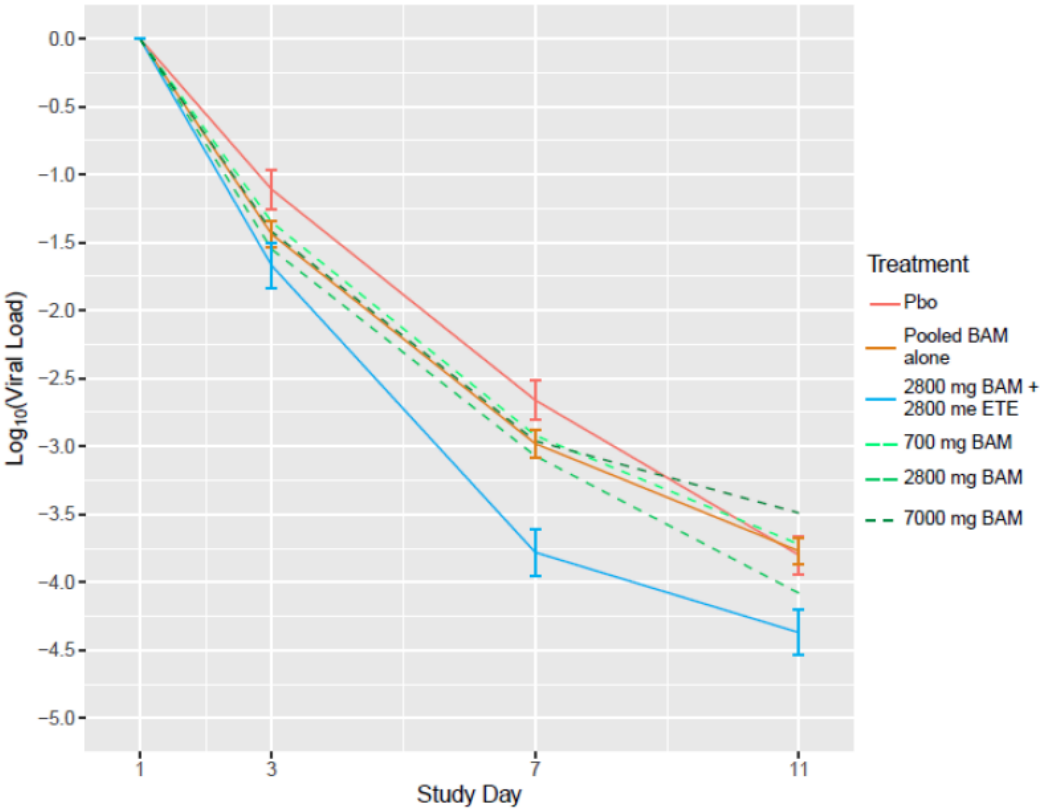
Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: EUA Request Tables 8.2, 8.5, and 8.10.

*Virologic Outcomes*

The prespecified primary efficacy endpoint was change from baseline to Day 11 (±4) in SARS-CoV-2 viral load. The Agency agreed with this endpoint for this study originally designed as a phase 2 dose finding trial. For phase 3 trials, FDA generally recommends the use of clinical endpoints reflecting how a patient feels, functions, and survives. Secondary virologic endpoints included change from baseline to Day 11 (±4) in SARS-CoV-2 viral load in participants enrolled with ≤8 days of symptoms prior to randomization; the proportion of participants that achieved SARS-CoV-2 clearance (Days 7, 11, 15, and 22); and time to SARS-CoV-2 clearance.

Results for the primary endpoint at Day 11 showed significantly greater reductions from baseline in SARS-CoV-2 viral load in the bamlanivimab and etesevimab group than in the placebo group (p = 0.01), as displayed in the figure below. However, the clinical meaningfulness of the Day 11 primary endpoint was unclear because most patients in the placebo group had largely cleared the virus by this timepoint.

**Figure 1: SARS-CoV-2 Viral Load Change from Baseline with Standard Errors in Trial PYAB (Treatment Arms 1-4 and 6)**




**Legend**

**Pbo** = placebo (Treatment Arm 1)

**Pooled BAM alone** = pooled data from

- 700 mg bamlanivimab (Treatment Arm 2)
- 2800 mg bamlanivimab (Treatment Arm 3), and
- 7000 mg bamlanivimab (Treatment Arm 4).

**700 mg BAM** = bamlanivimab 700 mg (Treatment Arm 2)

**2800 mg BAM** = bamlanivimab 2800 mg (Treatment Arm 3)

**7000 mg BAM** = bamlanivimab 7000 mg (Treatment Arm 4)

**2800 mg BAM + 2800 mg ETE** = 2800 mg bamlanivimab/2800 mg etesevimab (Treatment Arm 6).

Source: Regulatory Response submitted December 22, 2020, Figure 4.1.

The Applicant conducted additional analyses of virologic outcomes based on an observation from blinded data (i.e., pooled across treatment groups) that persistently high viral load at Day 7 correlated with hospitalization. Persistently high viral load was defined based on a cycle threshold value of 27.5 or less at Day 7. The following table shows that bamlanivimab and etesevimab led to a substantially lower rate of persistently high viral load than placebo.

**Table 6: Percentage of Participants with Persistently High[a] SARS-CoV-2 Viral Load at Day 7 in Trial PYAB (Treatment Arms 1-4 and 6)**

| Group | Events | Placebo – treatment difference | 95% CI[b] | p-value[c] |
|---|---|---|---|---|
| Placebo | 30/145 (21%) | | | |
| BAM 700 mg | 12/99 (12%) | 9% | -1% to 18% | 0.08 |
| BAM 2800 mg | 9/101 (9%) | 12% | 3% to 20% | 0.01 |
| BAM 7000 mg | 10/99 (10%) | 11% | 1% to 19% | 0.03 |
| BAM 2800 mg and ETE 2800 mg | 3/100 (3%) | 18% | 10% to 25% | <0.0001 |

[a] Defined as $\log_{10}$ viral load ≥ 5.27 (CT ≤ 27.5).
[b] Confidence intervals were from the Miettinen-Nurminen method.
[c] The two-sided p-values were from Fisher's exact test.
Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: EUA Request Table 8.3 and statistical reviewer.

*Clinical Outcomes*

While viral load was used to define the primary endpoint in this phase 2 trial, the most important evidence that bamlanivimab and etesevimab may be effective came from the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. This endpoint is considered a clinically meaningful outcome for outpatient studies, and reliable evidence of a treatment effect on this endpoint would provide a strong basis for efficacy conclusions. Mortality was also part of this composite endpoint, but no deaths were recorded for this secondary analysis in these phase 2 data. Although there were only 15 participants with events across Treatment Arms 1-4 and 6, the table below shows that bamlanivimab and etesevimab led to a nominally significantly lower event rate than placebo for this composite endpoint. Likewise, participants receiving bamlanivimab alone (pooled across doses) had nominally significantly lower event rates than participants randomized to placebo. These findings were referred to as "nominally" statistically significant because the study did not adjust for multiplicity in considering multiple secondary endpoints and the multiple active treatment groups.

**Table 7: COVID-19-Related Hospitalizations or Emergency Room Visits Within 28 Days After Treatment in Trial PYAB (Treatment Arms 1-4 and 6)**

| Group | Events | Placebo – treatment difference | 95% CI[a] | p-value[b] |
|---|---|---|---|---|
| Placebo | 9/156 (6%) | | | |
| BAM 700 mg | 1/101 (1%) | 5% | 0% to 10% | 0.09 |
| BAM 2800 mg | 2/107 (2%) | 4% | -1% to 9% | 0.21 |
| BAM 7000 mg | 2/101 (2%) | 4% | -2% to 9% | 0.21 |
| Pooled Mono | 5/309 (2%) | 4% | 1% to 9% | 0.02 |
| BAM 2800 mg and ETE 2800 mg | 1/112 (1%) | 5% | 0% to 10% | 0.05 |
| Pooled treatment arms | 6/421 (1%) | 4% | 1% to 9% | <0.01 |

[a] Confidence intervals were from the Miettinen-Nurminen method.

[b] The two-sided p-values were from Fisher's exact test.
Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: EUA Request Table 8.6 and statistical reviewer.

These efficacy data did not show a dose-response relationship, as the estimated event rate in all active treatment groups was between 1% and 2%. Available data also demonstrate similar viral load reduction between a dosage of bamlanivimab 700 mg and etesevimab 1400 mg administered together and a dosage of bamlanivimab 2800 mg and etesevimab 2800 mg administered together (see Virologic Outcomes for Trial PYAH (BLAZE-4) below), which indicates that this dosage range is on the plateau of the exposure-response relationship and reflects near-maximal activity. The lack of a dose-response relationship for COVID-19 related hospitalizations or emergency room visits, along with the flat exposure-response relationship for viral load reduction and pharmacokinetic/ pharmacodynamic modeling (see Section XI), supports emergency use authorization of the bamlanivimab 700 mg and etesevimab 1400 mg dose regimen.

The Applicant also conducted an exploratory subgroup analysis showing that most COVID-19-related hospitalizations or emergency room visits occurred in patients classified as high risk for hospitalization. The high risk subgroup was defined according to ≥65 years of age, BMI ≥35 kg/$m^2$, chronic kidney disease, diabetes, immunosuppressive disease, or current receipt of immunosuppressive treatment. Participants were also considered high risk if they were ≥55 years of age and had at least one of cardiovascular disease, hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease.

**Table 8: COVID-19-Related Hospitalizations or Emergency Room Visits in Participants Who Were at Higher Risk of Hospitalization in Trial PYAB (Treatment Arms 1-4 and 6)**

| Group | Events | Placebo – treatment difference | 95% CI[a] | p-value[b] |
|---|---|---|---|---|
| Placebo | 7/68 (10%) | | | |
| BAM 700 mg | 1/46 (2%) | 8% | -2% to 18% | 0.14 |
| BAM 2800 mg | 1/45 (2%) | 8% | -2% to 18% | 0.14 |
| BAM 7000 mg | 2/44 (5%) | 6% | -6% to 16% | 0.48 |
| Pooled Mono | 4/135 (3%) | 7% | 1% to 17% | 0.05 |
| BAM 2800 mg and ETE 2800 mg | 1/38 (3%) | 8% | -4% to 18% | 0.25 |

[a] Confidence intervals were from the Miettinen-Nurminen method.
[b] The two-sided p-values were from Fisher's exact test.
Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: EUA Request Table 8.10 and statistical reviewer.

The listing below displays characteristics of participants with COVID-19-related hospitalizations or emergency room visits. As there were only 15 participants with these clinical events across all arms, efficacy conclusions

for Treatment Arms 1-4 and 6 would not necessarily be robust to small changes in event counts due to missing data or adjudications. COVID-19-related hospitalization occurred for 7 participants in the placebo group and no participants administered bamlanivimab and etesevimab together.

**Table 9: Listing of Patients with COVID-19-Related Hospitalizations or Emergency Room Visits in Trial PYAB (Treatment Arms 1-4 and 6)**

| Treatment | Age | BMI | Sex | Rand. Date | Event Start Date | Type of Event | Reason |
|---|---|---|---|---|---|---|---|
| Placebo | 47 | 38 | M | 22-Jul-20 | (b) (6) | ER | Worsening COVID-19 symptoms |
| Placebo | 36 | 35 | F | 24-Jul-20 | | Hosp. | Respiratory failure and sepsis |
| Placebo | 62 | 51 | M | 27-Jul-20 | | Hosp. ICU | Lung infection |
| Placebo | 48 | 32 | M | 11-Aug-20 | | ER | Nasal congestion |
| Placebo | 74 | 32 | F | 17-Aug-20 | | ER Hosp. | Hypoxemia and dehydration |
| Placebo | 53 | 26 | M | 26-Aug-20 | | Hosp. | COVID-19-related pneumonia |
| Placebo | 46 | 35 | M | 24-Aug-20 | | Hosp. | Shortness of breath |
| Placebo | 71 | 38 | F | 26-Aug-20 | | Hosp. | Shortness of breath |
| Placebo | 40 | 39 | M | 03-Sep-20 | | ER Hosp. | Bronchitis, renal insufficiency |
| BAM 700 mg | 86 | 23 | M | 16-Jul-20 | | Hosp. | Hypoxia due to COVID-19 |
| BAM 2800 mg | 39 | 29 | M | 11-Aug-20 | | ER Hosp. | COVID-19-related symptoms |
| BAM 2800 mg | 79 | 27 | M | 17-Aug-20 | | ER Hosp. | Weakness, shortness of breath |
| BAM 7000 mg | 39 | 35 | F | 24-Jul-20 | | Hosp. | Pneumonia |
| BAM 7000 mg | 74 | 31 | F | 27-Jul-20 | | ER Hosp. | Pneumonia |
| BAM 2800 mg and ETE 2800 mg | 20 | 18 | F | 03-Sep-20 | | ER | COVID-19, dehydration |

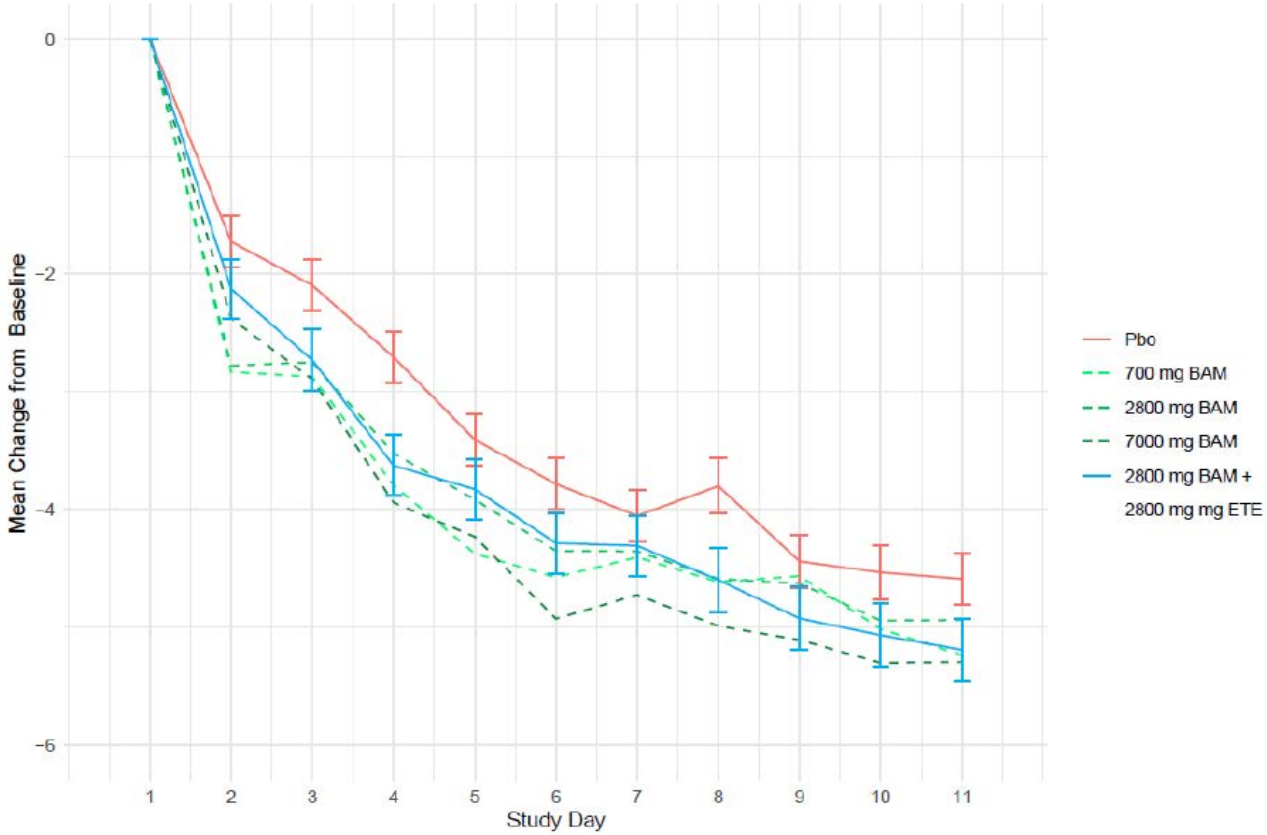
Abbreviations: BAM = bamlanivimab; BMI = body mass index; ER = emergency room visit; ETE = etesevimab; Hosp. = hospitalization; ICU = intensive care unit; Rand. = randomization.
Source: EUA Request 8.9

Additional predefined secondary endpoints were based on symptom measurements, although it is currently unclear what symptom-based endpoint would be optimal for COVID-19 outpatient trials. Patients used a daily questionnaire to rate various symptoms as 0 = none or absent, 1 = mild, 2 = moderate, or 3 = severe. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Secondary endpoints included time to

symptom resolution (i.e., symptoms scored as absent); symptom improvement at Days 7, 11, 15, and 22; and change from baseline in total symptom score (i.e., total rating) at Days 7, 11, 15, and 22.

The following figure displays mean changes from baseline over time in average symptoms for different treatment groups. The bamlanivimab and etesevimab group had a lower time weighted average symptom score than the placebo group (p = 0.003). However, the clinical meaningfulness of the aggregate symptom score was unclear. Differences in the time course of symptom resolution were not apparent between any of the active treatment groups.

**Figure 2: Mean Symptom Score Change from Baseline by Visit with Standard Errors in Trial PYAB (Treatment Arms 1-4 and 6)**

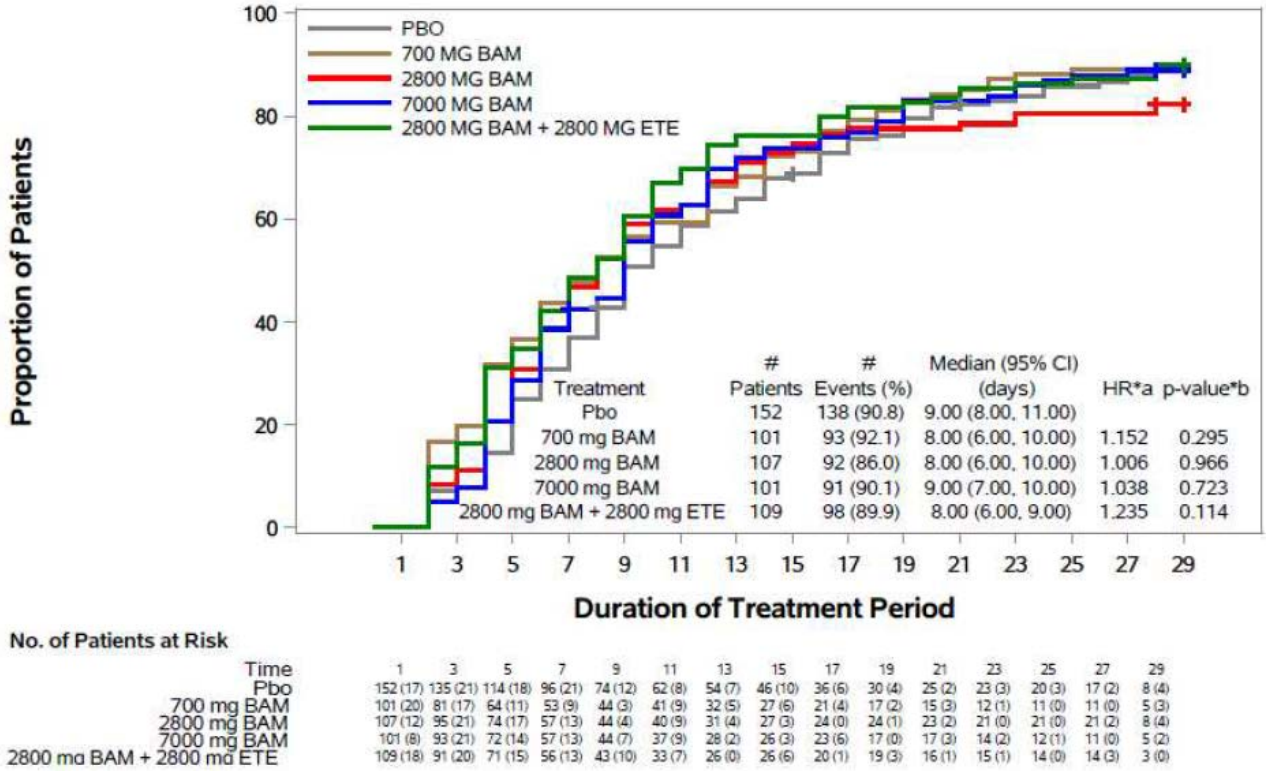



Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: Regulatory Response submitted December 22, 2020, Figure 4.2

The median time to symptom improvement was 6 days for bamlanivimab and etesevimab versus 8 days for placebo. Symptom improvement was defined as all symptoms scored as moderate or severe at baseline being scored as mild or absent, and all symptoms scored as mild or absent at baseline being scored as absent.

The figure below displays results for the endpoint of time to complete resolution of all 8 COVID-19 symptoms. Resolution times appeared relatively similar between placebo (9 day median) and bamlanivimab and etesevimab (8 day median). This trial was not designed to assess whether treatment could reduce rates of persistent or late symptoms after the acute stage of illness.

**Figure 3: Time to First Symptomatic Resolution, Kaplan Meier Product Limit Curve, Efficacy Population in Trial PYAB (Treatment Arms 1-4 and 6)**




No. of Patients at Risk

| Time | 1 | 3 | 5 | 7 | 9 | 11 | 13 | 15 | 17 | 19 | 21 | 23 | 25 | 27 | 29 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pbo | 152 (17) | 135 (21) | 114 (18) | 96 (21) | 74 (12) | 62 (8) | 54 (7) | 46 (10) | 36 (6) | 30 (4) | 25 (2) | 23 (3) | 20 (3) | 17 (2) | 8 (4) |
| 700 mg BAM | 101 (20) | 81 (17) | 64 (11) | 53 (9) | 44 (3) | 41 (9) | 32 (5) | 27 (6) | 21 (4) | 17 (2) | 15 (3) | 12 (1) | 11 (0) | 11 (0) | 5 (3) |
| 2800 mg BAM | 107 (12) | 95 (21) | 74 (17) | 57 (13) | 44 (4) | 40 (9) | 31 (4) | 27 (3) | 24 (0) | 24 (1) | 23 (2) | 21 (0) | 21 (0) | 21 (2) | 8 (4) |
| 7000 mg BAM | 101 (8) | 93 (21) | 72 (14) | 57 (13) | 44 (7) | 37 (9) | 28 (2) | 26 (3) | 23 (6) | 17 (0) | 17 (3) | 14 (2) | 12 (1) | 11 (0) | 5 (2) |
| 2800 mg BAM + 2800 mg ETE | 109 (18) | 91 (20) | 71 (15) | 56 (13) | 43 (10) | 33 (7) | 26 (0) | 26 (6) | 20 (1) | 19 (3) | 16 (1) | 15 (1) | 14 (0) | 14 (3) | 3 (0) |

Notes: Patients at risk displayed under Day x are calculated based on patients whose time to event or censoring >Day x date. Number of events displayed under Day x are calculated based on events that occurred during the time interval from Day x (excluding Day x date) to the day of next reported Day y (including Day y date).
*a HR - stratified by duration since symptom onset to randomization.
*b Stratified log-rank for comparison with placebo.
Abbreviations: BAM = bamlanivimab; CI = confidence interval; ETE = etesevimab; HR = hazard ratio.
Source: Regulatory Response submitted December 22, 2020, Figure 4.3.

*Analyses by Time Since Symptom Onset*

The mean duration of symptoms prior to treatment was 5 days in all active treatment groups and the placebo group. Approximately 96% of patients were treated within 10 days of symptom onset. At the request of DAV, additional analyses were conducted by the Applicant to determine if there were clinically significant trends or differences in outcomes based on time from symptom onset to the time of IV infusion  Evaluations of data for time from symptom onset were completed for Days 3, 5, and 7.  Given that high risk individuals were a smaller subset of the overall enrolled population,

there were limited data for these analyses; the samples were not powered to detect differences in the various endpoints based on time from symptom onset. There were, however, no notable differences in outcomes when considering time from symptom onset and percentage of patients with persistently high viral load at Day 7, COVID-19-related hospitalizations or ER visits, and change from baseline in SARS-CoV-2 viral load or change from baseline in total symptom score. As such, bamlanivimab and etesevimab are authorized for administration as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

*Summary of Efficacy Data in Treatment Arms 1-4 and 6*
Overall, Trial PYAB Treatment Arms 1-4 and 6 provided initial evidence that bamlanivimab and etesevimab may be effective for the treatment of high risk COVID-19 outpatients. In addition to favorable results for bamlanivimab and etesevimab in the prespecified primary analysis of viral load, a potential benefit was seen for the secondary endpoint of COVID-19-related hospitalizations or emergency room visits, which is clinically meaningful and is considered both an individual patient and public health benefit. Results were also suggestive of reduced symptom burden through Day 11. Clinical efficacy results did not show a dose-response relationship. The lack of a dose-response, along with the available pharmacokinetic and pharmacodynamic data (see Section XI), supports use of the bamlanivimab 700 mg dose administered together with 1400 mg etesevimab.

Limitations to the phase 2 efficacy data from Trial PYAB Treatment Arms 1-4 and 6 included multiplicity issues when considering favorable secondary endpoints and multiple dosing regimens, comparisons with the placebo group that were not fully concurrently randomized, the relatively small number of hospitalization events, and statistical uncertainty surrounding the number needed to treat to prevent serious clinical worsening.

Efficacy Results for Trial PYAB Treatment Arms 7-8 (Phase 3 - Topline Data)

Treatment Arms 7-8 of Trial PYAB compared bamlanivimab 2800 mg and etesevimab 2800 mg versus placebo. This analysis was considered similar to a phase 3 trial. This comparison was intended to confirm the preliminary efficacy signals seen in Treatment Arms 1-4 and 6 and provide more reliable evidence through use of a larger sample size, fully concurrent randomization, avoidance of multiplicity issues stemming from multiple dose groups, and prespecification of a clinical primary endpoint rather than virologic primary endpoint. Although results from Treatment Arms 7-8 provided stronger evidence of efficacy than the phase 2 results

from Treatment Arms 1-4 and 6, they are presented in less detail below because the submission was limited to topline data.

The main change in inclusion/exclusion criteria for Treatment Arms 7-8 was that enrollment was restricted to participants at high risk for progression to severe COVID-19 disease (using the previously described high risk criteria). High risk adolescents could also be enrolled if they were 12-17 years of age and had at least one of the following: BMI ≥85$^{th}$ percentile for age and sex based on CDC criteria; sickle cell disease; congenital or acquired heart disease; neurodevelopmental disorder such as cerebral palsy; medical-related technological dependence such as tracheostomy; asthma or reactive airway or other chronic respiratory disease requiring daily medication; type 1 or type 2 diabetes; chronic kidney disease; immunosuppressive disease; current receipt of immunosuppressive treatment.

A total of 1035 participants were enrolled in Treatment Arms 7-8. The table below displays baseline demographics and disease characteristics. The treatment group and the placebo group were generally well balanced on baseline factors. Approximately half of participants were female, 30% were Hispanic or Latino, and slightly under 10% of participants were Black or African American. Participants had been symptomatic for an average of 4 days before the baseline visit.

**Table 10: Baseline Demographics and Disease Characteristics in Trial PYAB (Treatment Arms 7-8)**

| | **Placebo (N = 517)** | **BAM 2800 mg and ETE 2800 mg (N = 518)** |
|---|---|---|
| Female | 259 (50%) | 279 (54%) |
| Hispanic or Latino | 155 (30%) | 149 (29%) |
| Black or African American | 39 (8%) | 44 (9%) |
| Age (median years) | 56 | 57 |
| Age ≥65 years | 155 (30%) | 168 (32%) |
| BMI (mean kg/m$^2$) | 33 | 34 |
| Mild COVID-19 | 403 (78%) | 397 (77%) |
| Moderate COVID-19 | 114 (22%) | 121 (23%) |
| Durations of symptoms (days, mean) | 4 | 4 |
| Viral load (mean, CT value) | 24 | 24 |

Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: BLAZE-1 Data Readout submitted to IND 150440 on January 25, 2020, Slide 2.

The prespecified primary efficacy endpoint was COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29. This was considered a clinically meaningful endpoint. The table below shows that the event rate in the placebo arm (7%) was significantly higher than the rate in the bamlanivimab 2800 mg and etesevimab 2800 mg arm (2%). The difference in event rates corresponded to an estimated number needed to treat of approximately 21

high risk outpatients to prevent one event. The 95% confidence interval for the difference in event rates corresponded to a number needed to treat between 13 and 42 patients. This reduction in COVID-19-related hospitalizations likely represents a major clinical benefit. If also considering COVID-19-related emergency room visits in addition to hospitalizations, then only one additional participant in each group would have been counted as having had an event.

**Table 11: COVID-19-Related Hospitalization or Death by any Cause by Day 29 in Trial PYAB (Treatment Arms 7-8)**

| Placebo | BAM 2800 mg and ETE 2800 mg | Placebo – treatment difference | 95% CI[a] | p-value |
|---|---|---|---|---|
| 36/517 (7%) | 11/518 (2%) | 5% | 2% to 8% | <0.001 |

[a] The confidence intervals was from the Miettinen-Nurminen method.
Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: Statistical reviewer and BLAZE-1 Data Readout submitted to IND 150440 on January 25, 2020, Slide 6.

The next table shows that all 10 deaths occurred in the placebo group. Thus, all-cause mortality was significantly lower in the bamlanivimab 2800 mg and etesevimab 2800 mg group than the placebo group. Only 1 of the 10 deaths was considered unrelated to COVID-19. The difference in mortality rates corresponded to an estimated number needed to treat of approximately 52 high risk outpatients to prevent 1 death, with a nominal 95% confidence interval for the number needed to treat between 28 and 95 high risk outpatients.

**Table 12: Death by Any Cause by Day 29 in Trial PYAB (Treatment Arms 7-8)**

| Placebo | BAM 2800 mg and ETE 2800 mg | Placebo – treatment difference | 95% CI[a] | p-value[b] |
|---|---|---|---|---|
| 10/517 (2%) | 0/518 (0%) | 2% | 1% to 4% | <0.001 |

[a] The Confidence interval was from the Miettinen-Nurminen method.
[b] The two-sided p-value was from Fisher's exact test.
Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: Statistical reviewer and BLAZE-1 Data Readout submitted to IND 150440 on January 25, 2020, Slide 9.

Significant treatment effects for bamlanivimab 2800 mg and etesevimab 2800 mg were also seen for the key secondary efficacy endpoints of viral load change from baseline to Day 7 ($p<0.001$), persistently high viral load at Day 7 (29% on placebo versus 10% on treatment; $p<0.001$), and time to sustained symptom resolution defined as two consecutive assessments with all symptoms absent except mild cough or fatigue (median 9 days for placebo versus 8 days for treatment; $p<0.01$). Symptom resolution at Day 11 was achieved for 61% of participants treated with bamlanivimab and etesevimab versus 52% for placebo ($p<0.01$).

In summary, Treatment Arms 7 and 8 demonstrated that bamlanivimab 2800 mg and etesevimab 2800 mg leads to major clinical benefits in preventing high risk outpatients with COVID-19 from progressing to hospitalization or death. Based on PK and PD data (see Section XI), lower doses of bamlanivimab 700 mg and etesevimab 1400 mg would also provide a similar clinical benefit. Therefore, based on the totality of scientific evidence, which includes the PK and PD data, the review team supports the recommendation to authorize this lower dosage than what was studied in Treatment Arms 7 and 8.

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Trial PYAB remains ongoing with additional treatment groups being assessed to compare and optimize doses. PYAB Treatment Arms 8 and 9 are evaluating bamlanivimab 700 mg and etesevimab 1400 mg administered together compared to placebo, in patients with mild to moderate COVID-19 who are at high risk for progression to more severe COVID-19 disease. Unblinded comparative results are not yet available for these additional groups that are intended to provide additional data to support the dosage of bamlanivimab 700 mg and etesevimab 1400 mg administered together.

Virologic Outcomes for Trial PYAH (BLAZE-4)

Trial PYAH (BLAZE-4, clinicaltrials.gov identifier NCT04634409) is an ongoing randomized, double-blind, placebo-controlled, phase 2 study evaluating different doses of bamlanivimab and etesevimab. Inclusion criteria specified that participants were to be adults who were not hospitalized, had at least one mild or moderate COVID-19 symptom, and had a positive SARS-CoV-2 test ≤3 days before the start of treatment. This trial did not enrich for high risk participants and excluded those ≥65 years old or with BMI ≥35.

The first 6 Treatment Arms in this trial were as follows. All treatments were given as single dose infusions.

- Treatment Arm 1: Placebo
- Treatment Arm 2: Bamlanivimab (b) (4) and etesevimab (b) (4)
- Treatment Arm 3: Bamlanivimab 700 mg and etesevimab 1400 mg
- Treatment Arm 4: Bamlanivimab 2800 mg and etesevimab 2800 mg
- Treatment Arm 5: Bamlanivimab 700 mg
- Treatment Arm 6: Bamlanvimab (b) (4) and etesevimab (b) (4)

The initially planned sample size was 100 participants per group. However, because Treatment Arm 6 began enrollment after other groups, there was a 50% increase for Treatment Arms 1 and 3 to ensure a sufficient number of concurrently randomized controls for this group. Virologic results are not yet complete for Treatment Arms 2 and 6.

Consequently, this review describes virologic results for the remaining groups. Results for clinical outcomes have not yet been submitted.

The median age was 39 years (with 1% of subjects aged 65 or older); 50% of subjects were female, 87% were White, 29% were Hispanic or Latino, and 6% were Black or African American; 8% of subjects were considered at high risk for disease progression. Participants had mild (84%) to moderate (16%) COVID-19; the mean duration of prior symptoms was 4 days; mean viral load by cycle threshold (CT) was 25 at baseline. The baseline demographics and disease characteristics were considered well balanced across treatment groups.

The primary efficacy endpoint in this trial was persistently high SARS-CoV-2 viral load at Day 7 (+2 days). As in Trial PYAB this was defined as $\log_{10}$ viral load >5.27. Rates of persistently high viral load were as follows:

- Placebo: 42/135 (31%)
- Bamlanivimab 700 mg and etesevimab 1400 mg: 21/147 (14%), p<0.001 versus placebo
- Bamlanivimab 2800 mg and etesevimab 2800 mg: 10/99 (10%), p<0.001 versus placebo
- Bamlanivimab 700 mg: 15/102 (15%), p<0.01 versus placebo

Thus, active treatment reduced rates of persistently high viral load at Day 7 compared with placebo. The numerical differences in rates between the active doses were consistent with chance variation. Secondary endpoints in this study included changes from baseline in SARS-CoV-2 viral load at Days 3, 5, and 7. At each of these timepoints, there was a numerically greater average change from baseline in viral load cycle threshold in the group treated with bamlanivimab 700 mg and etesevimab 1400 mg than in the group treated with bamlanivimab 2800 mg and etesevimab 2800 mg. Hence, although clinical outcome data are not yet available, the virologic results in this trial give additional support for authorization of bamlanivimab 700 mg and etesevimab 1400 mg.

Clinical Virology - Analysis of Spike Protein Variants

RNA extracted from nasopharyngeal samples collected at baseline and post-treatment was analyzed by next-generation sequencing (NGS). All baseline and emergent variants detected in ≥1 participant at allele frequencies of ≥15% and ≥50% were tabulated alongside viral shedding and clinical outcome data. An analysis of putative resistance-associated variants in clinical trials PYAA and PYAB (BLAZE-1) focused on amino acid positions in the receptor binding domain of the SARS-CoV-2 spike protein which had been identified in non-clinical studies as being important for susceptibility to either mAb: E484, F490, Q493 and S494 for

bamlanivimab, K417, D420 and N460 for etesevimab. Viral sequencing and phenotypic analyses are ongoing for clinical Trial PYAB.

Treatment-emergent substitutions were detected at spike protein amino acid positions K417, D420, N460, E484, F490, and S494, and included K417N, D420N, N460T, E484A/D/K/Q/V, F490L/S/V, and S494L/P (Table 13). Only K417N, D420N, N460T, E484D/K/Q, F490S, and S494P have been assessed phenotypically to date: F490S and S494P variants had reduced susceptibility to bamlanivimab in a SARS-CoV-2 neutralization assay of >485-fold and >91-fold, respectively, E484K and E484Q variants had reduced susceptibility to bamlanivimab in a pseudovirus neutralization assay of >2,360-fold and >890-fold, respectively, and E484D had a reduction in susceptibility to bamlanivimab in an ACE2 binding inhibition assay of >118-fold; D420N had a reduction in susceptibility to etesevimab in a SARS-CoV-2 neutralization assay of >1,593-fold, and K417N and N460T had reductions in susceptibility to etesevimab in pseudovirus neutralization assays of >6-fold and>21-fold, respectively. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of E484K and E484Q, which had reduced susceptibility of 15-fold and 22-fold, respectively, in a pseudovirus assay.

For the variants with phenotypic data, each was present in the GISAID database at a frequency of <0.25% (K417N, 0.1653%; D420N, 0.0003%; E484D, 0.0020%, E484K, 0.2405%; E484Q, 0.0146%, F490S, 0.0180%; S494P, 0.1145%; of total 405,416 deposited sequences as of 24 Jan 2021).

**Table 13. Treatment-Emergent Spike Substitutions at Amino Acid Positions of Known Bamlanivimab or Etesevimab Resistance Detected at an Allelic Frequency of ≥15%**

| Protein Change [a] | GISAID Frequency (N) [b] | Frequency (N) | | | | |
|---|---|---|---|---|---|---|
| | | Placebo | BAM 700 mg | BAM 2800 mg | BAM 7000 mg | BAM 2800 mg and ETE 2800 mg |
| K417N | 0.1653% (670) | 0% (0/145) | 0% (0/98) | 0% (0/102) | 0% (0/97) | 1.0% (1/102) |
| D420N | 0.0003% (1) | 0% (0/145) | 0% (0/98) | 1.0% (1/102) | 0% (0/97) | 0% (0/102) |
| N460T | 0.0005% (2) | 0% (0/145) | 0% (0/98) | 0% (0/102) | 0% (0/97) | 1.0% (1/102) |
| E484A | 0.0032% (13) | 0% (0/145) | 1.0% (1/98) | 0% (0/102) | 2.1% (2/97) | 0% (0/102) |
| E484D | 0.0020% (8) | 0% (0/145) | 1.0% (1/98) | 0% (0/102) | 0% (0/97) | 0% (0/102) |
| E484K | 0.2405% (975) | 2.8% (4/145) | 2.0% (2/98) | 5.9% (6/102) | 8.2% (8/97) | 0% (0/102) |
| E484Q | 0.0146% (59) | 1.4% (2/145) | 3.1% (3/98) | 5.9% (6/102) | 2.1% (2/97) | 0% (0/102) |
| E484V | 0.0002% (1) | 0% (0/145) | 0% (0/98) | 1.0% (1/102) | 0% (0/97) | 0% (0/102) |
| F490L | 0.0069% (28) | 0.7% (1/145) | 0% (0/98) | 1.0% (1/102) | 0% (0/97) | 1.0% (1/102) |
| F490S | 0.0180% (73) | 0% (0/145) | 0% (0/98) | 2.0% (2/102) | 0% (0/97) | 0% (0/102) |
| F490V | 0.0012% (5) | 0.7% (1/145) | 0% (0/98) | 0% (0/102) | 0% (0/97) | 0% (0/102) |
| S494L | 0.0049% (20) | 0% (0/145) | 1.0% (1/98) | 1.0% (1/102) | 2.1% (2/97) | 0% (0/102) |

| | | | | | | |
|---|---|---|---|---|---|---|
| S494P | 0.1145% (464) | 0.7% (1/145) | 2.0% (2/98) | 1.0% (1/102) | 2.1% (2/97) | 1.0% (1/102) |
| All | NA | 6.2% (9/145) | 9.2% (9/98) | 12.7% (13/102) | 15.5% (15/97) | 3.9% (4/102) |

N = number of participants that had nasal samples with positive RT-PCR and passed next generation sequencing quality control criteria

[a] Only K417N, D420N, D460T for etesevimab, E484D/K/Q, F490S, and S494P for bamlanivimab have been assessed phenotypically to date

[b] Frequency determined from 405,416 total number of spike sequences as of 24 January 2021.

Abbreviations: BAM = bamlanivimab; ETE = etesevimab

Source: Clinical resistance summary submitted with EUA request Table 5.7

Phenotypically confirmed bamlanivimab- or etesevimab-resistant variants in baseline samples were infrequent: (0% 0/14) in clinical study PYAA and 0.4% (2/523) in clinical Trial PYAB (Treatment Arms 1 to 4 and 6). Considering all substitutions detected at positions K417, D420, N460, E484, F490, and S494, 9.2% (9/98) and 6.1% (6/98) of participants in the 700-mg bamlanivimab arm harbored such a variant post-baseline at ≥15% and ≥50% allele fractions, respectively (Table 14). For bamlanivimab and etesevimab administered together, substitutions at these positions were detected at frequencies of 3.9% (4/102) and 0% (0/102) at ≥15% and ≥50% allele fractions, respectively. When the genotypic analysis was restricted to high-risk participants, in the 700 mg bamlanivimab arm, variants were detected at frequencies of 14.0% (6/43) and 9.3% (4/43) for ≥15% and ≥50% allele fractions, respectively; no variants were detected in the bamlanivimab and etesevimab arm.

The majority of the emergent variants were first detected on Day 7 following treatment initiation and some were detected in individuals at more than one time point (4/9 and 4/6 for the bamlanivimab 700-mg arm, at ≥15% and ≥50% allele fractions, respectively, and 0/4 for the bamlanivimab and etesevimab arm, at ≥15% allele fraction).

**Table 14. Bamlanivimab and Etesevimab Treatment-Emergent Resistance-Associated Substitutions at Positions D420, N460, E484, F490, and S494**

| | PBO | BAM 700 mg | BAM 2800 mg | BAM 7000 mg | BAM 2800 mg and ETE 2800 mg |
|---|---|---|---|---|---|
| All Participants ≥15% VAF | 6.2% (9/145) | 9.2% (9/98) | 12.7% (13/102) | 15.5% (15/97) | 3.9% (4/102) |
| All Participants ≥50% VAF | 3.4% (5/145) | 6.1% (6/98) | 6.9% (7/102) | 11.3% (11/97) | 0% (0/102) |
| Only Single Time Point Detection ≥15% VAF | 9/9 | 5/9 | 7/13 | 7/15 | 4/4 |
| Only Single Time Point Detection ≥50% VAF | 5/5 | 2/6 | 1/7 | 4/11 | 0/0 |
| High-Risk Participant ≥15% VAF | 3.1% (2/65) | 14.0% (6/43) | 23.8% (10/42) | 22.7% (10/44) | 0% (0/33) |
| High-Risk Participant ≥50% VAF | 1.5% (1/65) | 9.3% (4/43) | 14.3% (6/42) | 18.2% (8/44) | 0% (0/33) |

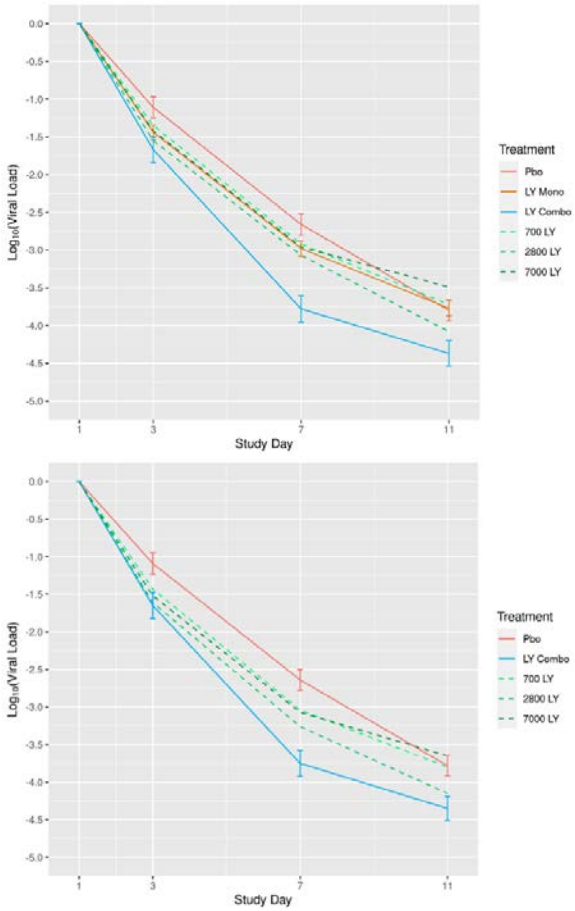
Abbreviations: BAM = bamlanivimab; ETE = etesevimab

Source: EUA request

Change in viral load was analyzed excluding all treated subjects in whom a treatment-emergent bamlanivimab resistance-associated spike protein

variant was detected (Figure 4). Numerically greater reduction in viral load by the monotherapy was observed on study Days 3 and 7 when compared with the analysis of all patients. The clinical relevance of this observation is not known.

**Figure 4. SARS-CoV-2 Viral Load Change from Baseline by Visit (with Standard Error). Left: All treated subjects; Right: Data with exclusion of subjects with Phenotypically Confirmed Bamlanivimab-Resistant Variants.**




Abbreviations: BAM = bamlanivimab; ETE = etesevimab
Source: EUA request Figure 8.13

With respect to clinical outcomes for subjects in whom resistance-associated variants were detected, for the pooled bamlanivimab monotherapy arms, 3/37 subjects in whom a treatment-emergent resistance-associated variant was detected at ≥15% allele fraction experienced hospitalization for COVID-19. For the placebo arm, and bamlanivimab and etesevimab arm, 0/9 and 0/4 subjects, respectively, in whom a resistance-associated variant was detected experienced a hospitalization or emergency room visit. Overall, there were too few hospitalization or emergency room visits in subjects harboring resistance-associated variants to draw firm conclusions. Analyses of treatment-

emergent resistance in clinical studies are ongoing, including for Treatment Arms 7 and 8 of PYAB.

## IX. Clinical Safety

Across the clinical development program as of January 23, 2021, approximately 1500 participants have received bamlanivimab and etesevimab administered together (bamlanivimab 2800 mg and etesevimab 2800 mg, n = 730; bamlanivimab 700 mg and etesevimab 1400 mg, n = 770). More than 3900 participants have received an IV infusion of bamlanivimab alone or with etesevimab at doses ranging from 700 to 7000 mg.

The November 2020 EUA request included complete safety data on Treatment Arms 1-4 and 6 from Trial PYAB (BLAZE-1) with follow up on all subjects for a minimum of 29 days. Additional topline safety data through Day 29, providing deaths, SAEs, and adverse events following a database lock on January 20, 2021 from Treatment Arms 7 and 8 were submitted to the EUA on January 25, 2021 and are reviewed separately below.

Trial PYAB - Treatment Arms 1-4 and 6 (Phase 2) Safety Results

*Exposure for Safety Analysis*

Treatment Arms 1-4 and 6 includes data from 577 subjects dosed with 700 mg (n = 101), 2800 mg (n =107), 7000 mg (n = 101) of bamlanivimab alone, bamlanivimab 2800 mg and etesevimab 2800 mg, administered together (n = 112), or placebo (n = 156). These subjects were treated and then followed for a minimum of 29 days. The reviewed safety data reflects a database lock on November 4, 2020. 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 placebo, bamlanivimab, and bamlanivimab and etesevimab treatment groups. The majority of AEs were mild to moderate in severity. The majority of events were mild and moderate AEs. There were no deaths nor any discontinuations due to AEs in treatment arms 1-4 and 6 of Trial PYAB (Table 15).

**Table 15: Summary of Adverse Events in Trial PYAB (Treatment Arms 1-4 and 6)**

| N (%) | Placebo (N = 156) | BAM 700 mg (N = 101) | BAM 2800 mg (N = 107) | BAM 7000 mg (N = 101) | BAM 2800 mg and ETE 2800 mg (N = 112) |
|---|---|---|---|---|---|
| Any AEs | 44 (28%) | 29 (29%) | 26 (24%) | 24 (24%) | 20 (18%) |
| AEs by severity | | | | | |
| Mild | 23 (15%) | 18 (18%) | 17 (16%) | 11 (11%) | 15 (13%) |
| Moderate | 18 (12%) | 7 (7%) | 7 (7%) | 8 (8%) | 4 (4%) |
| Severe | 3 (2%) | 3 (3%) | 2 (2%) | 5 (5%) | 1 (1%) |
| Deaths | 0 | 0 | 0 | 0 | 0 |
| SAEs | 1 (1%) | 1 (1%) | 0 | 0 | 1 (1%) |
| DCs due to AEs | 0 | 0 | 0 | 0 | 0 |

Mild=mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated; moderate=moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated; Severe=severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.
Abbreviations: AE = adverse event; BAM = bamlanivimab, DC = discontinuation of study drug; ETE = etesevimab, SAE = serious adverse event;
Source: EUA Request Table 8.11

Common adverse events reported in Trial PYAB included the preferred terms (PTs) nausea, pruritus, diarrhea, dizziness, rash, vomiting, and pyrexia. The incidence of these events was comparable across placebo and treatment arms (Table 16).

**Table 16: Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥1% of All Patients in Trial PYAB (Treatment Arms 1-4 and 6)**

| N (%) | Placebo (N = 156) | BAM 700 mg (N = 101) | BAM 2800 mg (N = 107) | BAM 7000 mg (N = 101) | BAM 2800 mg and ETE 2800 mg (N = 112) |
|---|---|---|---|---|---|
| Nausea | 6 (4%) | 3 (3%) | 4 (4%) | 4 (4%) | 4 (4%) |
| Pruritus | 1 (1%) | 2 (2%) | 3 (3%) | 0 (0%) | 2 (2%) |
| Diarrhea | 7 (5%) | 1 (1%) | 1 (1%) | 5 (5%) | 1 (1%) |
| Dizziness | 3 (2%) | 3 (3%) | 3 (3%) | 3 (3%) | 1 (1%) |
| Rash | 1 (1%) | 1 (1%) | 0 (0%) | 1 (1%) | 1 (1%) |
| Vomiting | 4 (3%) | 1 (1%) | 3 (3%) | 1 (1%) | 1 (1%) |
| Pyrexia | 0 (0%) | 1 (1%) | 2 (2%) | 1 (1%) | 1 (1%) |
| Headache | 3 (2%) | 3 (3%) | 2 (2%) | 1 (1%) | 0 (0%) |
| Chills | 0 (0%) | 0 (0%) | 1 (1%) | 3 (3%) | 0 (0%) |
| Hypertension | 1 (1%) | 1 (1%) | 0 (0%) | 3 (3%) | 0 (0%) |
| Blood pressure increased | 0 (0%) | 3 (3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Chest discomfort | 1 (1%) | 0 (0%) | 1 (1%) | 2 (2%) | 0 (0%) |
| Dyspnea | 0 (0%) | 1 (1%) | 1 (1%) | 1 (1%) | 0 (0%) |
| Fatigue | 0 (0%) | 0 (0%) | 1 (1%) | 2 (2%) | 0 (0%) |
| Lipase increased | 0 (0%) | 1 (1%) | 0 (0%) | 2 (2%) | 0 (0%) |
| Nasal congestion | 1 (1%) | 2 (2%) | 1 (1%) | 0 (0%) | 0 (0%) |
| Thrombocytosis | 0 (0%) | 1 (1%) | 2 (2%) | 0 (0%) | 0 (0%) |

Abbreviations: BAM = bamlanivimab, ETE = etesevimab
Source: EUA Request Table 8.12

Moderate treatment-emergent AEs were rarely reported in patients who received bamlanivimab and etesevimab. All events reported as moderate in the monoclonal treatment groups were singular (Table 17).

**Table 17: Moderate Treatment-Emergent Adverse Events by SOC and PT Occurring in ≥1% in at Least One Treatment Group in Trial PYAB (Treatment Arms 1-4 and 6)**

| System Organ Class<br>Preferred Term | Placebo<br>(N = 156) | BAM<br>700 mg<br>(N = 101) | BAM<br>2800 mg<br>(N = 107) | BAM<br>7000 mg<br>(N = 101) | BAM 2800 mg and<br>ETE 2800 mg<br>(N = 112) |
|---|---|---|---|---|---|
| **Gastrointestinal disorders** | **7 (5%)** | **1 (1%)** | **2 (2%)** | **3 (3%)** | **0 (0%)** |
| Nausea | 4 (3%) | 0 (0%) | 1 (1%) | 1 (1%) | 0 (0%) |
| Abdominal pain | 1 (1%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) |
| Diarrhea | 2 (1%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Dyspepsia | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Gastroesophageal reflux disease | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Vomiting | 3 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Musculoskeletal and connective tissue disorders** | **2 (1%)** | **2 (2%)** | **2 (2%)** | **1 (1%)** | **0 (0%)** |
| Back pain | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Musculoskeletal chest pain | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) |
| Myalgia | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Rheumatoid arthritis | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) |
| Spinal pain | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Arthralgia | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Neck pain | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Nervous system disorders** | **5 (3%)** | **2 (2%)** | **1 (1%)** | **2 (2%)** | **0 (0%)** |
| Dizziness | 1 (1%) | 1 (1%) | 1 (1%) | 1 (1%) | 0 (0%) |
| Presyncope | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Syncope | 1 (1%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Dysgeusia | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Headache | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tremor | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **General disorders and administration site conditions** | **0 (0%)** | **1 (1%)** | **0 (0%)** | **3 (3%)** | **0 (0%)** |
| Chest discomfort | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Chills | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Fatigue | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Swelling face | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Vascular disorders** | **0 (0%)** | **2 (2%)** | **0 (0%)** | **2 (2%)** | **1 (1%)** |
| Hypertension | 0 (0%) | 1 (1%) | 0 (0%) | 2 (2%) | 0 (0%) |

| | | | | | |
|---|---|---|---|---|---|
| Deep vein thrombosis | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Orthostatic hypotension | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| **Skin and subcutaneous tissue disorders** | **1 (1%)** | **0 (0%)** | **1 (1%)** | **2 (2%)** | **0 (0%)** |
| Cold sweat | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) |
| Rash | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Urticaria | 1 (1%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| **Infections and infestations** | **2 (1%)** | **0 (0%)** | **0 (0%)** | **2 (2%)** | **0 (0%)** |
| Urinary tract infection | 0 (0%) | 0 (0%) | 0 (0%) | 2 (2%) | 0 (0%) |
| Pelvic inflammatory disease | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Tonsillitis | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Investigations** | **0 (0%)** | **2 (2%)** | **0 (0%)** | **0 (0%)** | **1 (1%)** |
| Blood pressure increased | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hepatic enzyme increased | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 1 (1%) |
| **Immune system disorders** | **1 (1%)** | **1 (1%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** |
| Hypersensitivity | 1 (1%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Injury, poisoning, and procedural complications** | **0 (0%)** | **0 (0%)** | **1 (1%)** | **0 (0%)** | **1 (1%)** |
| Animal bite | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) |
| Skin laceration | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| **Metabolism and nutrition disorders** | **3 (2%)** | **0 (0%)** | **0 (0%)** | **1 (1%)** | **0 (0%)** |
| Hypophosphatemia | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Dehydration | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Diabetes mellitus | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Pregnancy, puerperium, and perinatal conditions** | **0 (0%)** | **0 (0%)** | **1 (1%)** | **0 (0%)** | **0 (0%)** |
| Pregnancy* | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) |
| **Psychiatric disorders** | **0 (0%)** | **0 (0%)** | **0 (0%)** | **1 (1%)** | **0 (0%)** |
| Insomnia | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| **Cardiac disorders** | **1 (1%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** |
| Ventricular extrasystoles | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Eye disorders** | **1 (1%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** |
| Eye pain | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Respiratory, thoracic and mediastinal disorders** | **2 (1%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** | **1 (1%)** |
| Atelectasis | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Cough | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Nasal Congestion | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Surgical and medical procedures** | **1 (1%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** |

| | | | | | |
|---|---|---|---|---|---|
| Thrombectomy | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

*Denominator adjusted to reflect gender-specific event for females (n=85 for placebo, n=63 for 700 mg, n=51 for 2800 mg, n=58 for 7000 mg, n=58 for 2800 LY combo)
Abbreviations: BAM = bamlanivimab, ETE = etesevimab
Source: FDA Reviewer, adapted from Regulatory Response (23Nov20_AE tables and hypersensitivity)

Severe AEs were rare across placebo and treatment arms. All severe AEs were reported as singular events (Table 18).

**Table 18: Severe Treatment-Emergent Adverse Events by SOC and PT Occurring in ≥1% in at Least One Treatment Group in Trial PYAB (Treatment Arms 1-4 and 6)**

| System Organ Class<br>Preferred Term | Placebo<br>(N = 156) | BAM<br>700 mg<br>(N = 101) | BAM<br>2800 mg<br>(N = 107) | BAM<br>7000 mg<br>(N = 101) | BAM 2800 mg and<br>ETE 2800 mg<br>(N = 112) |
|---|---|---|---|---|---|
| **Injury, poisoning, and procedural complications** | **0 (0%)** | **1 (1%)** | **1 (1%)** | **0 (0%)** | 0 (0%) |
| Maternal exposure during pregnancy* | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) |
| Joints injury | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Metabolism and nutrition disorders** | **0 (0%)** | **1 (1%)** | **1 (1%)** | **0 (0%)** | **0 (0%)** |
| Diabetic ketoacidosis | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hyperglycemia | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) |
| **Musculoskeletal and connective tissue disorders** | **0 (0%)** | **0 (0%)** | **0 (0%)** | **2 (2%)** | **0 (0%)** |
| Muscle spasm | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Neck pain | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| **Gastrointestinal disorders** | **2 (1%)** | **0 (0%)** | **0 (0%)** | **1 (1%)** | **1 (1%)** |
| Nausea | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 1 (1%) |
| Abdominal pain upper | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Hemorrhoids thrombosed | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Vomiting | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| **Investigations** | **0 (0%)** | **0 (0%)** | **0 (0%)** | **1 (1%)** | **0 (0%)** |
| Alanine aminotransferase increased | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| **Psychiatric disorders** | **0 (0%)** | **0 (0%)** | **0 (0%)** | **1 (1%)** | **0 (0%)** |
| Insomnia | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| **Renal and urinary disorders** | **0 (0%)** | **1 (1%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** |
| Renal mass | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |

| | | | | | |
|---|---|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | **1 (1%)** | **1 (1%)** | **0 (0%)** | **0 (0%)** | **0 (0%)** |
| Dyspnea | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Asthma | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Surgical and medical procedures** | **0 (0%)** | **0 (0%)** | **1 (1%)** | **0 (0%)** | **0 (0%)** |
| Abortion induced* | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) |

*Denominator adjusted to reflect gender-specific event for females (n=85 for placebo, n=63 for 700 mg, n=51 for 2800 mg, n=58 for 7000 mg, n=58 for 2800 LY combo)
Abbreviations: BAM = bamlanivimab, ETE = etesevimab
Source: FDA Reviewer, adapted from Regulatory Response (23Nov20_AE tables and hypersensitivity)

*Deaths*

As of the November 4, 2020 data lock, no deaths were reported in Treatment Arms 1-4 and 6.

*Serious Adverse Events*

Serious adverse events (SAEs) were reported in three participants in Trial PYAB in Treatment Arms 1-4 and 6:

- Upper abdominal pain was reported in a 64-year-old participant who received placebo. The SAE started on Day 7 and ended on Day 11.
- Diabetic ketoacidosis was reported in a 38-year-old participant with type 1 diabetes mellitus who received bamlanivimab 700 mg. The SAE occurred on Day 26 and resolved on Day 27.
- Urinary tract infection was reported in a 65-year-old participant who received bamlanivimab 2800 mg and etesevimab 2800 mg administered together. The SAE started on Day 14 and was ongoing at the time of database lock on Day 30.

*Laboratory Findings*

Treatment-emergent hematologic laboratory abnormalities were considered clinically significant if they were grade 3 and associated with a clinical AE or were grade 4 by the Common Terminology Criteria for Adverse Events (CTCAE). Four events of clinically significant decreases in absolute neutrophil count were reported (placebo n=1, bamlanivimab 2800 mg n=2, bamlanivimab 7000 mg n=1). One participant who received bamlanivimab 2800 mg and etesevimab 2800 mg administered together was noted to have a clinically significant decrease in absolute lymphocyte count. Most of these events occurred on Day 2 or Day 3 following treatment. These decreases were not associated with other clinically significant treatment-emergent cytopenias.

Abnormalities in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were considered clinically significant if they led to additional testing, per protocol, with associated clinical AEs reported. In Trial PYAB, three clinically significant increases (one patient with increases in ALT and AST, one patient with increases in ALT, and one patient with increase in AST) occurred in patients who received bamlanivimab 2800 mg and etesevimab 2800 mg administered together. The elevations all resolved and were not associated with other clinically significant laboratory abnormalities. In addition, an increase in ALT was considered to be severe in a patient who received bamlanivimab 7000 mg.

Other notable laboratory findings include hyperglycemia (bamlanivimab 2800 mg n=1), which was considered severe and hypophosphatemia (bamlanivimab 7000 mg n=1) which was considered moderate in severity. Overall, there was no drug-related pattern of laboratory abnormalities.

*Long-Term Follow-Up Safety for Treatment Arms 1-4 and 6 in Trial PYAB*

Additional information was requested to determine if there were any clinically significant safety findings in patients followed for a longer period of time.

In an update submitted to the EUA on January 24 2021, the Sponsor indicated that as of the December 31, 2020 database lock, across PYAB arms 1-4 and 6, more than 91% of subjects had at least 85 days of post-dose follow-up (placebo 89%; bamlanivimab 700 mg 89%; bamlanivimab 2800 mg 96%; bamlanivimab 7000 mg 94%; bamlanivimab 2800 mg and etesevimab 2800 mg administered together, 87%). Eighteen (6%) subjects who received bamlanivimab alone, seven (6%) subjects who received bamlanivimab and etesevimab together, and six (4%) of placebo subjects reported at least one adverse event during the follow-up period. The majority of the adverse events reported in the follow-up period were mild or moderate. There were no apparent patterns of clinically significant adverse events in the long-term follow-up safety analyses.

<u>Trial PYAB Treatment Arms 7-8 (Phase 3) Topline Safety Results</u>

*Exposure for Safety Analysis*

Patients with mild to moderate COVID-19 with risk factors for progression to severe illness and/or hospitalization were enrolled in Treatment Arms 7 and 8. In Treatment Arm 7, 518 subjects were randomized to bamlanivimab 2800 mg and etesevimab 2800 mg administered together, while 517 subjects were randomized to placebo in Treatment Arm 8

Topline safety data were obtained from all subjects for the first 29 days of the trial and reflect data from a database lock on January 20, 2021.

*Adverse Events*

Adverse Events (AEs) occurred at comparable rates across Treatment Arms 7 and 8. Most events were mild or moderate in severity. As all COVID-19 related deaths were counted as endpoints, only non-COVID-19 related deaths were to be counted as AEs. There was one non-COVID-19 related death in the placebo group, which resulted in discontinuation due to AE.

**Table 19: Summary of Adverse Events in Trial PYAB (Treatment Arms 7-8)**

| N (%) | Placebo (N = 517) | BAM 2800 mg and ETE 2800 mg (N = 518) |
|---|---|---|
| Any AEs | 60 (12%) | 69 (13%) |
| AEs by severity | | |
| Mild | 35 (7%) | 37 (7%) |
| Moderate | 20 (4%) | 24 (5%) |
| Severe | 5 (1%) | 7 (1%) |
| Deaths | 1 (0%) | 0 (0%) |
| SAEs | 5 (1%) | 7 (1%) |
| DCs due to AEs | 1 (0%) | 0 (0%) |

Mild=mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated; moderate=moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated; Severe=severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.
Abbreviations: AE = adverse event; BAM = bamlanivimab, DC = discontinuation of study drug; ETE = etesevimab, SAE = serious adverse event;
Source: BLAZE-1 Data Readout submitted to IND 150440 on January 25, 2020, Slide 3.

Common adverse events reported in Treatment Arms 7 and 8 included the following PTs: nausea, rash, and dizziness. These events were similar to what was reported in Treatment Arms 1-4 and 6. The incidence of these events was comparable across placebo and treatment arms (Table 20).

**Table 20: Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥1% of All Patients in Trial PYAB (Treatment Arms 7-8)**

| N (%) | Placebo (N = 517) | BAM 2800 mg and ETE 2800 mg (N = 518) |
|---|---|---|
| Nausea | 4 (1%) | 5 (1%) |
| Rash | 3 (1%) | 6 (1%) |
| Dizziness | 3 (1%) | 4 (1%) |

Abbreviations: BAM = bamlanivimab, ETE = etesevimab
Source: BLAZE-1 Data Readout submitted to IND 150440 on January 25, 2020, Slide 4.

*Deaths*

As of January 20, 2021, 10 deaths were reported in the placebo Treatment Arm 8. Of these deaths, 9 were considered to be COVID-19 related and one was considered an AE. The non-COVID-19 related AE death occurred in a 59-year-old man with a BMI of 61 who died on Day 3 post-infusion. No additional details are available at this time. Of note, no deaths were reported in participants that received bamlanivimab and etesevimab administered together in Treatment Arm 7.

*Serious Adverse Events*

Serious adverse events (SAEs) were reported in 5 (1%) participants randomized to placebo and 7 (1%) to participants randomized to bamlanivimab and etesevimab. A listing of all SAEs is included in Table 21. All events were singular. While there is an imbalance in Cardiac Disorders events between bamlanivimab 2800 mg and etesevimab 2800 mg administered together compared to placebo, the difference was not statistically significant (p-value 0.124).

**Table 21: Serious Adverse Events by System Organ Class and Preferred Term in Trial PYAB (Treatment Arms 7-8)**

| N (%) | Placebo (N = 517) | BAM 2800 mg and ETE 2800 mg (N = 518) |
|---|---|---|
| **Cardiac disorders** | **0 (0%)** | **4 (1%)** |
| Acute myocardial infarction | 0 (0%) | 1 (0%) |
| Atrial fibrillation | 0 (0%) | 1 (0%) |
| Atrial flutter | 0 (0%) | 1 (0%) |
| Ventricular extrasystoles | 0 (0%) | 1 (0%) |
| **Metabolism and nutrition disorders** | **2 (0%)** | **1 (0%)** |
| Hyperglycemia | 1 (0%) | 1 (0%) |
| Dehydration | 1 (0%) | 0 (0%) |
| **Gastrointestinal Disorders** | **1 (0%)** | **0 (0%)** |
| Abdominal Pain | 1 (0%) | 0 (0%) |
| **General disorders and administration site conditions** | **1 (0%)** | **0 (0%)** |
| Sudden death | 1 (0%) | 0 (0%) |
| **Injury, poisoning and procedural complications** | **0 (0%)** | **1 (0%)** |
| Toxicity to various agents | 0 (0%) | 1 (0%) |
| **Investigations** | **0 (0%)** | **1 (0%)** |
| Catheterization cardiac | 0 (0%) | 1 (0%) |
| **Nervous system disorders** | **1 (0%)** | **0 (0%)** |
| Syncope | 1 (0%) | 0 (0%) |
| **Renal and urinary disorders** | **0 (0%)** | **1 (0%)** |
| Acute kidney injury | 0 (0%) | 1 (0%) |
| **Reproductive system and breast disorders** | **0 (0%)** | **1 (0%)** |
| Menorrhagia | 0 (0%) | 1 (0%) |

| | | |
|---|---|---|
| **Respiratory, thoracic, and mediastinal disorders** | **0 (0%)** | **1 (0%)** |
| Hypoxia | 0 (0%) | 1 (0%) |

Abbreviations: BAM = bamlanivimab, ETE = etesevimab
Source: BLAZE-1 Data Readout submitted to IND 150440 on January 25, 2020, Slide 5.

Analysis of Submission-Specific Safety Issues

*Hypersensitivity and Infusion-Related Reactions*

A common reaction to intravenously-administered monoclonal antibodies is hypersensitivity, including infusion reactions. To identify potential infusion-related AEs, an analysis using narrow and broad terms within the Hypersensitivity Standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) was completed by Eli Lilly. In Treatment Arms 1-4 and 6, the proportion of hypersensitivity reactions was similar across treatment arms and did not occur more frequently in higher dose groups (Table 22).

**Table 22: Hypersensitivity Events by Severity in Trial PYAB (Treatment Arms 1-4 and 6)**

| | **Placebo (N = 156)** | **BAM 700 mg (N = 101)** | **BAM 2800 mg (N = 107)** | **BAM 7000 mg (N = 101)** | **BAM 2800 mg and ETE 2800 mg (N = 112)** |
|---|---|---|---|---|---|
| Mild | 6 (3%) | 5 (5%) | 7 (7%) | 4 (4%) | 3 (3%) |
| Moderate | 3 (2%) | 2 (2%) | 0 (0%) | 3 (3%) | 0 (0%) |
| Severe | 1 (1%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |

Mild=mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated; moderate=moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated; Severe=severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.
Abbreviations: BAM = bamlanivimab, ETE = etesevimab
Source: Regulatory Response (25Nov20_Safety-Hypersensitivity Clarification); table generated by FDA Reviewer

Hypersensitivity events were defined as immediate if they occurred within 24 hours of administration of trial medication or placebo. There was no dose dependence across Treatment Arms 1-4 and 6 for immediate hypersensitivity events and most reactions were considered to be mild, including the two events that occurred in patients who received bamlanivimab and etesevimab administered together (Table 23).

**Table 23: Hypersensitivity Events by Severity in Trial PYAB that Occurred Within 24 Hours of Infusion (Treatment Arms 1-4 and 6)**

| | **Placebo (N = 156)** | **BAM 700 mg (N = 101)** | **BAM 2800 mg (N = 107)** | **BAM 7000 mg (N = 101)** | **BAM 2800 mg and ETE 2800 mg (N = 112)** |
|---|---|---|---|---|---|
| Mild | 1 (1%) | 1 (1%) | 5 (5%) | 0 (0%) | 2 (2%) |
| Moderate | 0 (0%) | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |

| | | | | | |
|---|---|---|---|---|---|
| Severe | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

Source: Regulatory Response (25Nov20_Safety-Hypersensitivity Clarification); table generated by FDA Reviewer
Mild=mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated; moderate=moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated; Severe=severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.
Abbreviations: BAM = bamlanivimab, ETE = etesevimab
Source: Regulatory Response (25Nov20_Safety-Hypersensitivity Clarification); table generated by FDA Reviewer

Immediate hypersensitivity events that occurred in Treatment Arms 1-4 and 6 were all mild events of flushing or pruritus, with the exception of one moderate event of facial swelling that occurred 8 hours post-dosing (Table 24).

**Table 24: Description of Hypersensitivity Events in Trial PYAB that Occurred Within 24 Hours of Infusion (Treatment Arms 1-4 and 6)**

| Subject ID | Age/Sex/ Race | Drug/Dose | PT (verbatim) | Severity | Time Post- Dose | Investigator Considered Drug Related | Action Taken with Drug |
|---|---|---|---|---|---|---|---|
| (b) (6) | 52/F/WH | 700mg | Pruritus (on arm by IV site) | Mild | 8 min | No | Drug Not Changed |
| | 27/F/WH | 700 mg | Face Swelling | Moderate | 484 min | Yes | Not Applicable |
| | 43/M/WH | 2800 mg | Pruritus | Mild | 28 min | Yes | Drug Interrupted |
| | 27/M/WH | 2800 mg | Pruritus | Mild | 26 min | Yes | Drug Not Changed |
| | 33/M/WH | 2800 mg | Flushing (face) | Mild | 1 min | Yes | Drug Not Changed |
| | 40/F/WH | 2800 mg | Hypersensitivity (mild allergic reaction flushing) | Mild | 0 min | Yes | Not Applicable |
| | 33/F/BL | 2800 mg | Chest tightness | Mild | 30 min | Yes | Drug Not Changed |
| | 43/M/WH | BAM and ETE | Pruritus (left arm) | Mild | 46 min | Yes | Drug Not Changed |
| | 20/F/WH | BAM and ETE | Pruritus (Right upper arm) | Mild | 70 min | Yes | Drug Not Changed |
| | 38/F/WH | PBO | Flushing (face) | Mild | 405 min | No | Drug Not Changed |

Abbreviations: PT= MedDRA preferred term; WH=white; F= female; M= male; BAM = bamlanivimab; ETE = etesevimab; PBO=placebo
Source: Regulatory Response (25Nov20_Safety-Hypersensitivity Clarification); table generated by FDA Reviewer

Hypersensitivity events that occurred beyond the 24-hours post-dose in Treatment Arms 1-4 and 6 are summarized in Table 25. In general, these events were mild to moderate, self-resolving, and most were not considered related to study drug administration.

**Table 25: Description of Hypersensitivity Events in Trial PYAB that Occurred Beyond 24 Hours of Infusion (Treatment Arms 1-4 and 6)**

| Subject ID | Age/Sex/ Race | Drug/Dose | PT (verbatim) | Severity | Study Day post-dose | Investigator Considered Drug Related | Action Taken |
|---|---|---|---|---|---|---|---|
| (b) (6) | 23/F/WH | 700 mg | Rash | Mild | 14 | No | Drug Not Changed |
| | 58/F/WH | 700 mg | Hypersensitivity (Allergic reaction – unknown cause) | Moderate | 4 | No | Not Applicable |
| | 32/F/WH | 700 mg | Pruritus, shortness of breath | Mild, Severe | 2, 55 | Yes, No | Drug Not Changed |
| | 28/M/WH | 700 mg | Cough | Mild | 84 | No | Drug Not Changed |
| | 38/F/AI | 700 mg | Right leg edema | Mild | 6 | No | Not Applicable |
| | 57/M/WH | 2800 mg | Pruritus | Mild | 10 | No | Drug Not Changed |
| | 40/F/WH | 2800 mg | Difficulty breathing | Mild | 25 | No | Drug Not Changed |
| | 32/F/WH | 7000 mg | Chest discomfort, Urticaria | Moderate | 2, 8 | No | Drug Not Changed |
| | 38/M/WH | 7000 mg | Stomatitis | Mild | 5 | No | Not Applicable |
| | 50/F/WH | 7000 mg | Rash (neck) | Moderate | 5 | Yes | Not Applicable |
| | 23/M/WH | 7000 mg | Chest discomfort, cough, shortness of breath | Mild | 36, 73, 78 | No | Drug Not Changed |
| | 62/M/WH | BAM and ETE | Rash (calves) | Mild | 18 | No | Drug Not Changed |
| | 24/F/WH | PBO | Pruritus | Mild | 7 | No | Not Applicable |
| | 52/F/AI | PBO | Rash | Mild | 3 | Not recorded | Not Applicable |
| | 37/F/WH | PBO | Hypersensitivity (Allergic reaction – unknown cause) | Moderate | 7 | No | Not Applicable |
| | 52/F/WH | PBO | Urticaria, Asthma | Moderate, Severe | 2, 13 | No | Not Applicable |
| | 53/M/WH | PBO | Conjunctivitis | Mild | 3 | No | Drug Not Changed |
| | 40/M/WH | PBO | Contact dermatitis | Mild | 22 | No | Not Applicable |
| | 40/M/WH | PBO | Cough | Moderate | 25 | No | Not Applicable |
| | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (b) (6) | 41/F/MU | PBO | Chest discomfort | Mild | 20 | No | Not Applicable |

Abbreviations: BAM= bamlanivimab, ETE= etesevimab
Source: Regulatory Response (25Nov20_Safety-Hypersensitivity Clarification); table generated by FDA Reviewer
PT= MedDRA preferred term; WH=white; F= female; M= male; PBO=placebo

Additional safety data for Treatment Arms 7 and 8 of PYAB, reflecting a database lock on January 20, 2021, was submitted to the EUA on January 27, 2021. Immediate hypersensitivity reactions that occurred on the day of study drug administration were identified using narrow and broad terms within the Hypersensitivity standardized MedDRA query. One event, erythema, was reported in the placebo group; six events (1%) were identified in the cohort that received bamlanivimab 2800 mg and etesevimab 2800 mg. Events identified in the treatment group included infusion related reaction (n = 2; moderate), rash (n = 2; 1 mild, 1 moderate), infusion site rash (n = 1; mild), and pruritus (n=1; mild). Additional events of dyspnea (n =1; mild) and respiratory failure (n = 1; severe) were also reported at 595 minutes and 567 minutes, respectively, though it is unclear if these events were related to infusion or to clinical worsening of COVID-19 infection.

*Serious Hypersensitivity Events Including Anaphylaxis in Overall Safety Database*

More severe infusion-related hypersensitivity or anaphylactic events, including three SAEs have occurred during or following infusion of bamlanivimab at doses above 700 mg in other ongoing clinical trials. In order to better assess the risk of infusion-related reactions, DAV requested that the Applicant unblind two of the four events that occurred during infusion.

Infusion-related SAEs during infusion:

- In ACTIV-2, a Grade 3 infusion reaction was reported in a 20-year old female participant with a history of exercise-induced asthma and anxiety. This reaction, marked by difficulty breathing and redness (flushing), occurred 7 minutes after the start of the infusion (b) (4). The infusion was discontinued, and the subject received intramuscular epinephrine and diphenhydramine orally and the symptoms resolved. The subject was sent for further evaluation at the emergency room but did not require hospitalization.
- In Trial PYAD, an 18-year old male with a history of migraines developed a runny nose, swelling of the right eye, and throat swelling 10 minutes after the start of infusion of bamlanivimab 4200 mg. The infusion was stopped, and the subject received intravenous diphenhydramine and steroids and the symptoms

resolved. The subject was evaluated in the emergency room but did not require hospitalization.

- In Trial PYAH, a 33-year old female participant with no notable medical history developed facial flushing, swollen lips and chest/back pain approximately 3 minutes after the initiation of the *blinded trial medication* infusion. The infusion was stopped, intravenous diphenhydramine was administered, and the hypersensitivity reaction resolved. The patient was discharged home from the study site.
- In Trial PYAH, a 56-year old female participant with past medical history of back pain developed weakness in her chest, a sensation of burning in her throat, and dizziness approximately 8 minutes after the initiation of infusion of *blinded trial medication*. The infusion was stopped, and the patient received diphenhydramine with subsequent resolution of symptoms.

Infusion-related SAEs after infusion:

- In ACTIV-3, a 50-year old female with a history of chronic renal failure, renal transplant, obesity, diabetes, who was hospitalized with COVID-19 experienced temperature increase, chills, headache, and body aches approximately three and half hours after receiving *blinded trial medication*. Of note, this patient was neutropenic and was receiving ertapenem. The patient received acetaminophen and diphenhydramine. She was placed on 1L nasal cannula for tachypnea but was not considered to be short of breath or hypoxic and did not have chest pain, rash, or hives.

While most reported infusion reactions were mild or moderate in severity, more severe reactions have been observed (see *Safety Monitoring After Bamlanivimab Alone EUA)*. In order to mitigate risks of severe infusion reactions, bamlanivimab 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. Patients should be clinically monitored during infusion and observed for at least 1 hour after infusion is complete.

*Safety Monitoring After Bamlanivimab Alone EUA*

As part of Emergency Use Authorization for bamlanivimab, health care providers must submit reports of all medication errors and serious adverse events potentially related to bamlanivimab. These data are continually reviewed by the Division of Pharmacovigilence (DPV) and DAV. Following review of 518 cases submitted to the FAERS database, revisions were made to the Health Care Provider Fact Sheet for bamlanivimab to more

accurately reflect the available safety information. Specifically, new signs and symptoms were added to Section 5.1 Warning: Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions including: difficulty breathing, reduced oxygen saturation, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status and diaphoresis. Additionally, based on review of cases with reports of clinical worsening after administration of bamlanivimab, DAV and DPV agreed that a new section should be added to the warning to make HCPs aware that clinical worsening after treatment has been reported and could occur. Therefore, a new Warning: Clinical Worsening After Bamlanivimab Administration in Section 5.2 was added. However, many of the cases were confounded due to underlying morbidities, age or other factors and it is challenging to determine if the clinical worsening was a result of administration of bamlanivimab or due to progression of COVID-19. Modifications consistent with these changes were also added to the Patient Fact Sheet.

The changes in Sections 5.1 and 5.2 in the Fact Sheets for bamlanivimab authorized on January 28, 2021 are also included in the Fact Sheets for EUA 94 in Sections 5.1 and 5.2.

*Bamlanivimab Alone Treatment of COVID-19 in Hospitalized Patients – ACTIV 3*

Bamlanivimab has been studied in hospitalized patients with COVID-19 in the phase 3 master protocol trial ACTIV-3, entitled: A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (NCT04501978). On October 13, 2020, the Data Safety Monitoring Board paused enrollment stating that a pre-defined safety boundary had been crossed. The FDA reviewed the unblinded DSMB data. On Day 5, there was evidence of clinical worsening when comparing ordinal outcomes in the two trial cohorts. The imbalance in worse clinical outcomes was more apparent in enrolled subjects who required high flow oxygen at baseline, which was the maximum amount of respiratory support permitted for subjects in this portion of the trial. Additionally, there was an increased incidence of grade 3 and grade 4 adverse events, SAEs, and deaths in one of treatment groups. The DSMB reviewed data from 314 participants on October 26, 2020 and concluded that there was not a statistically significant difference in grade 3 and grade 4 AEs, SAEs, and deaths on Day 5 nor through Day 28. They also determined that there was no statistically significant difference in deaths between the groups (7 in group A, 4 in group B, p=0.36). Re-evaluation of the Day 5 pulmonary outcome did not show worsening in clinical outcomes, but no benefit was seen. As such, bamlanivimab did not meet criteria to advance to the next stage of

the platform trial and the randomization of patients to bamlanivimab in this trial was not resumed.

Patients that were already randomized to treatment or placebo in ACTIV-3 will continue to be followed. The DSMB supported the continuation of ACTIV-2, which enrolls non-hospitalized patients with mild to moderate COVID-19 illness. At this time, there are no data showing benefit to support use of bamlanivimab in hospitalized patients. As such, clinicians should be aware of the lack of benefit demonstrated in the hospitalized patients with late stage severe COVID-19 and for the potential for worse clinical outcomes in this population.

In addition, the FDA was aware of a public statement from a DSMB overseeing a trial of another new drug in this class in hospitalized patients. The DSMB paused the enrollment of patients requiring high-flow oxygen or mechanical ventilation, based on a potential safety signal and unfavorable benefit risk profile.

Therefore, our review of the data supports inclusion of a Limitations of Authorized Use as follows:

**LIMITATIONS OF AUTHORIZED USE**

- 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.

*Antiviral Resistance*

While *in vitro* resistance studies identified amino acid substitutions within the spike receptor binding domain that conferred reduced susceptibility to bamlanivimab or etesevimab when either drug was tested alone, there was no effect on susceptibility when bamlanivimab and etesevimab were tested together, with the exception of variants harboring E484K, E484Q or Q493R substitutions.

When considering emergent variants following treatment in Arms 1-4 and 6, the presence of specific resistant variants were seen in both placebo and treatment groups. Notably, resistant variants were less frequently detected in patients who received bamlanivimab and etesevimab together compared to patients who received bamlanivimab alone or received placebo. This observation is likely due to the fact that bamlanivimab and etesevimab bind to different but overlapping epitopes in the receptor binding region of the S-protein. (For additional information, please see Section VIII, Clinical Efficacy).

Despite the low incidence of emergent resistant variants in participants who received bamlanivimab and etesevimab, there remains a theoretical risk that the emergence of resistant viral variants could lead to treatment failure. In addition, it is possible that an individual could be infected with a viral variant that is not neutralized by bamlanivimab alone or bamlanivimab and etesevimab administered together. New circulating isolates that may have enhanced transmissibility have been identified: B.1.1.7 (also known as the UK variant), B.1.351 (also known as the South African variant), and P1 (also known as B.1.1.28.1 or the Brazilian variant). Based on preliminary pseudovirus data, it is thought that bamlanivimab alone, as well as bamlanivimab and etesevimab together, retain neutralizing activity against variants harboring spike protein substitutions identified in isolate B.1.1.7, but that both bamlanivimab alone and etesevimab alone have reduced activity against variants harboring spike protein substitutions identified in isolate B.1.351. The Applicant is still conducting studies to determine if bamlanivimab or etesevimab have neutralizing activity against authentic SARS-CoV-2 variants. It is likely that individuals infected with B.1.351, and potentially P1, will not benefit from treatment with bamlanivimab alone nor bamlanivimab and etesevimab together, though clinical samples that confirm a COVID-19 diagnosis are not typically sequenced prior to administration of these monoclonals. The clinical decision to use bamlanivimab or bamlanivimab and etesevimab together should be made in the context of what is known about local prevalence of these variants at the time of treatment.

While assessment of resistance variants across the development program is ongoing, it is likely that the risk of the emergence of resistant variants from treatment with bamlanivimab and etesevimab together is low, or comparable to the risk for such an event to occur following natural infection. Nonetheless, it is recommended that patients 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.

*Immune Response Attenuation*

Administration of bamlanivimab and etesevimab may attenuate the endogenous immune response to SARS-CoV-2 and potentially make patients more susceptible to re-infection. Similarly, bamlanivimab and etesevimab administration could reduce the response to SARS-CoV-2 vaccination. In response to this potential risk, the Advisory Committee on Immunization Practices (ACIP) has issued interim recommendations related to the use of Pfizer-BioNTech and Moderna COVID-19 vaccines in individuals who have received passive antibody therapy such as bamlanivimab and etesevimab. While there are no data on the safety and efficacy of mRNA COVID-19 vaccines in persons who have received monoclonal antibodies as part of COVID-19 therapy, it is currently recommended that vaccination be deferred for at least 90 days. This recommendation is based upon the evidence that suggests that reinfection with COVID-19 is uncommon in the 90 days after initial infection as well as the estimated half-life of the available monoclonal antibodies.

*Anti-Drug Antibodies*

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. The risk of ADE for bamlanivimab and etesevimab assessed individually and together was addressed by the Applicant in non-clinical cell culture studies; the mAbs were also assessed individually in non-human primate studies (Please see Section XIII, Nonclinical Data to Support Efficacy for more information related to ADE). The applicability of the findings from these studies to the clinical setting is not known. While there was no clear evidence of enhanced disease in subjects treated with bamlanivimab and etesevimab in Trial PYAB, or in other trials in a similar population, there is still a theoretical possibility of increased incidence of reinfection or enhanced disease if infected again once mAb

concentrations have waned to sub-neutralizing concentrations in mAb-treated subjects.

## X. Specific Populations

Rationale for Inclusion of Pediatric Patients Under EUA

As of January 21, 2021 over 2.5 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 12.7% 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, and the similar PK in adolescents weighing ≥40 kg based on modeling, and the safety profile, 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 includes adolescents who are 12 years of age and older and who weigh at least 40 kg. As of February 4, 2021, 32 adolescent patients have been randomized to bamlanivimab and etesevimab administered together or placebo in Trial PYAB.

Dose Considerations for Specific Populations

- Safety and pharmacokinetic (PK) data are not available in children, pregnant women, lactating women, patients with renal insufficiency, or patients with moderate or severe hepatic insufficiency. No dosage adjustment is recommended based on age (18 to 86 years of age), sex, race, body weight (41 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 profiles of bamlanivimab and etesevimab are linear and dose-proportional between 700 mg and 7000 mg following single IV administration. There were no differences in PK of bamlanivimab between subjects with severe and moderate COVID-19 who were hospitalized and ambulatory subjects with mild and moderate COVID-19. There were no differences in PK of etesevimab between mild/moderate ambulatory participants and healthy participants. There is no difference in PK of bamlanivimab or etesevimab administered alone or together suggesting there is no interaction between the two antibodies.
- The PK of bamlanivimab and etesevimab were not affected by age (18 to 86 years of age), sex, race, or baseline viral load based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bamlanivimab in adults with COVID-19 over the body weight range of 41 to 173 kg.

Rationale for Dose Based on PK/PD

- In Study PYAH, a dosage of 700 mg bamlanivimab and 1400 mg etesevimab administered together and a dosage of 2800 mg bamlanivimab and 2800 mg etesevimab administered together produced similar viral load reductions, which indicates a flat exposure-response relationship for viral load reduction within this dose range.
- To provide additional support for the proposed dose of bamlanivimab and etesevimab, a PK/PD analysis was carried out to estimate the serum concentrations of bamlanivimab and etesevimab that were expected to achieve 90% of antiviral effect ($EC_{90}$) *in vivo*.
- The 700 mg bamlanivimab dose achieved serum concentrations above the *in vivo* $EC_{90}$ value of viral load reduction for at least 28 days in 90% of the patient population.
- The *in vivo* $EC_{90}$ of etesevimab is expected to be no more than 8-fold higher than the $EC_{90}$ of bamlanivimab based on comparison of the in vitro EC90 values of bamlanivimab and etesevimab and population PK-PD modeling.
- The 1400 mg etesevimab dose achieved serum concentrations above the expected *in vivo* $EC_{90}$ value of viral load reduction for at least 28 days in 90% of the patient population.
- Population PK-PD modeling supports antiviral effects of 700 mg bamlanivimab and 1400 mg etesevimab which are predicted to

provide sufficient efficacy margins of serum concentrations over *in vivo* $EC_{90}$ for at least 28 days after treatment (see Appendix XXVI.3 for details).

- The viral load reduction in the high risk patients (Defined under Section III, Proposed Use and Dosing of the Product Under the EUA) was estimated to be ~60% of the low risk patients. The proposed dose of bamlanivimab and etesevimab is expected to achieve near-maximal efficacy irrespective of risk strata.

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

- The PK of bamlanivimab and etesevimab were not affected by age (18 to 86 years of age), sex, race, disease severity (moderate/severe in PYAA [bamlanivimab] vs. mild/moderate in PYAB [bamlanivimab and etesevimab]) or baseline viral load based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bamlanivimab in adults with COVID-19 over the body weight range of 41 to 173 kg.
- Pediatric patients: The PK of bamlanivimab and etesevimab in pediatric patients have not been evaluated. Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after accounting for the effect of body size on PK. Using modeling and simulation, the authorized dosing regimen is expected to result in comparable plasma exposures of bamlanivimab and etesevimab in pediatric patients aged 12 years of age or older who weigh at least 40 kg as observed in adult patients.
- Patients with renal impairment: Bamlanivimab and etesevimab are not eliminated intact in the urine; thus, renal impairment is not expected to affect the exposures of either bamlanivimab or etesevimab.
- Patients with hepatic impairment: Mild hepatic impairment did not have a clinically meaningful effect on the PK of bamlanivimab or etesevimab. Neither bamlanivimab nor etesevimab have been studied in patients with moderate or severe hepatic impairment.

Drug-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.

## 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

Bamlanivimab and etesevimab were assessed in non-clinical studies of epitope mapping, binding, neutralization, effector function, resistance and antibody-dependent enhancement (ADE) of infection. ADE was assessed in cell culture and in an African green monkey model of SARS-CoV-2. Antiviral activity was assessed for both mAbs in a rhesus macaque prophylaxis model and as a treatment for etesevimab only. The animal models are not directly relevant to the treatment indication being sought for this EUA request of bamlanivimab and etesevimab administered together, so are only summarized here.

- Bamlanivimab bound to the SARS-CoV-2 spike protein and receptor binding domain (RBD) of the spike protein with $K_D$ = 0.071 nM and 2.2 nM, respectively, as determined using surface plasmon resonance (SPR). Similar experiments showed direct competition with the human angiotensin converting enzyme 2 (hACE2) receptor, with an $IC_{50}$ value of 0.17 nM (0.025 µg/mL). Etesevimab bound to the RBD with a $K_D$ = 6.45 nM, as determined by SPR. Etesevimab blocked the interaction between the hACE2 receptor and spike protein RBD with an $IC_{50}$ value of 0.32 nM (0.046 µg/mL).

- An analysis of the crystal structure of the bamlanivimab Fab:RBD complex indicated that bamlanivimab makes close contacts with residues 351, 449-450, 455-456, 470, 472, 481-489, and 492-494 of the S protein. The etesevimab conformational epitope on SARS-CoV-2 RBD was determined by X-ray crystallography of the etesevimab:SARS-CoV-2 RBD co-structure, which indicated that etesevimab interacts with the following SARS-CoV-2 RBD residues: R403, D405, E406, R408, Q409, T415, G416, K417, D420, Y421, L455, F456, R457, K458, S459, N460, Y473, Q474, A475, G476, S477, F486, N487, Y489, Q493, Y495, N501, G502, G504, and Y505.

- The cell culture neutralization activity of bamlanivimab and etesevimab against SARS-CoV-2 was measured in a dose-response model quantifying plaque reduction using cultured Vero E6 cells. Bamlanivimab had an estimated mean $EC_{50}$ value = 0.14 nM (0.02 µg/mL) and $EC_{90}$ value of 0.55 nM (0.08 µg/mL) against the USA/WA/1/2020 clinical isolate of SARS-CoV-2, and an estimated $EC_{50}$ value of 0.34 nM (0.05 µg/mL) and $EC_{90}$ value of 1.78 nM (0.26 µg/mL) against the Italy-INMI1 clinical isolate. Etesevimab had an estimated neutralization $EC_{50}$ value of 0.97 nM (0.14 µg/mL) against the USA/WA/1/2020 clinical isolate of SARS-CoV-2, and an $EC_{50}$ value = 0.83 nM (0.12 µg/mL) and $EC_{90}$ value of 12.8 nM (1.86 µg/mL) against the Italy-INMI1 clinical isolate. Using a 1:1 (weight/weight) ratio, bamlanivimab and etesevimab together had a neutralization $EC_{50}$ value of 0.14 nM (0.02 µg/mL) and $EC_{90}$ value of 0.76 nM (0.11 µg/mL) against the USA/WA/1/2020 isolate, and an $EC_{50}$ value of 0.41 nM (0.06 µg/mL) and $EC_{90}$ value of 2.1 nM (0.30 µg/mL) against the Italy-INMI1 isolate.

- Serial passage of SARS-CoV-2 in cell culture in the presence of bamlanivimab identified virus harboring spike protein substitutions F490S and S494P as having reduced susceptibility (>485-fold and >91-fold, respectively) to bamlanivimab SARS-CoV-2 neutralization. Serial passage of SARS-CoV-2 in cell culture in the presence of etesevimab identified virus harboring spike protein substitutions D420N

and N460K as having reduced susceptibility (>1,593-fold and >129-fold, respectively) to etesevimab SARS-CoV-2 neutralization. Additional variant substitutions detected at an allele frequency <50% included E484D for bamlanivimab (reduced susceptibility to bamlanivimab in an ACE2 binding inhibition assay of >118-fold), and K417N, N460T and N460Y for etesevimab (reduced susceptibility to etesevimab in a pseudovirus assay of >6-fold, >21-fold and >210-fold, respectively). Yeast display library studies identified additional variant RBD proteins, E484K, E484Q and Q493R for bamlanivimab and N460S for etesevimab. The E484K, E484Q and Q493R variants had reduced susceptibility to bamlanivimab in pseudovirus neutralization assays of >2,360-fold, 890-fold and >6,666-fold, respectively, and the N460S variant had reduced susceptibility to etesevimab in a pseudovirus neutralization assay of >302-fold. The Q493R variant also had reduced susceptibility to etesevimab (232-fold) in a pseudovirus assay. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of those with E484K, E484Q, and Q493R substitutions, which had reduced susceptibility of 15-fold, 22-fold, and >100-fold, respectively, in a pseudovirus assay. Selection of resistance to bamlanivimab and etesevimab when tested together was not successful, and no variants were identified using three different SARS-CoV-2 isolates up to 10 successive passages or using directed evolution with yeast display.

- Pseudoviral 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 22-fold, respectively, but activity was maintained with bamlanivimab alone, and with bamlanivimab and etesevimab together. Pseudovirus harboring spike substitutions K417N + E484K + N501Y together had reduced susceptibility to bamlanivimab or etesevimab alone of >60-fold and >23-fold, respectively, indicating that bamlanivimab and etesevimab together are likely to have reduced activity against viral variants harboring these concurrent substitutions, such as those from B.1.351 (South African origin). Studies are in process to test the activity of bamlanivimab and etesevimab together against additional pseudoviruses from this lineage and the related P.1 (Brazilian origin) lineage.

- Bamlanivimab demonstrated antibody-dependent cell-mediated cytotoxicity (ADCC) on reporter Jurkat cells expressing FcγRIIIa upon engagement by CHO cells stably co-expressing spike protein and human CD20. Bamlanivimab did not elicit complement-dependent cytotoxicity (CDC) activity in cell-based assays. Etesevimab did not

demonstrate detectable ADCC activity on Jurkat reporter cells expressing FcγRIIIa. Etesevimab did not elicit CDC activity in cell-based assays.

- The risk of antibody-dependent enhancement (ADE) by bamlanivimab or etesevimab was evaluated in cell culture. The risk of ADE by bamlanivimab preincubated with SARS-CoV-2 was evaluated in Thp1, Raji and ST486 cell lines and human primary macrophages. Overall, there was no clear evidence of enhanced viral uptake or productive infection across cell lines and experiments, but there were instances of increased intracellular and extracellular viral RNA levels relative to control IgG1 seen in Raji and THP1 cells at 30 ng/mL and 3,000 ng/mL of bamlanivimab. The ability of etesevimab to mediate enhanced pseudovirus transduction was evaluated in Raji cells or 293 cells expressing FcγRI, FcγRIIA-H131, FcγRIIAR131, FcγRIIB, or FcγRIIIA-V158. No enhanced SARS-CoV-2 pseudovirus infection was observed. Two further studies were conducted in which immune cells (primary macrophages, THP1, and Raji) were tested for their ability to support viral SARS-CoV-2 replication in the presence of etesevimab at concentrations ranging from 1 to 10,000 ng/mL or from 0.0003 to 3,000 ng/mL, respectively. Overall, and across cell lines, an increase in intracellular or extracellular RNA was not observed in the presence of etesevimab relative to the IgG1 controls. In similar experiments conducted using bamlanivimab and etesevimab together, there was no clear evidence of ADE across the cell lines tested.

- An African green monkey model of SARS-CoV-2 infection was used to determine whether bamlanivimab or etesevimab mediated ADE *in vivo* by assessing viral shedding in animals treated prophylactically at sub-neutralizing or neutralizing doses (0.05 mg/kg or 20 mg/kg, respectively, of either bamlanivimab or etesevimab). For bamlanivimab, comparing viral shedding/load differences in nasal and oral swabs, bronchoalveolar lavage, and lung tissue between bamlanivimab and IgG1 isotype control animals, there did not appear to be evidence of ADE. For etesevimab, overall, there were no statistically significant increases in viral loads in etesevimab-treated animals when compared with IgG1-LALA control.

- The ability of bamlanivimab to reduce viral load following pre-exposure prophylactic treatment was evaluated *in vivo* using a rhesus macaque SARS-CoV-2 infection model (n=3 or 4 per group), using a single IV dose of bamlanivimab one day prior to challenge with SARS-CoV-2. Bamlanivimab resulted in 1 to 4 $\log_{10}$ decreases in viral load (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. The ability of etesevimab to reduce viral load following prophylactic or therapeutic treatment was evaluated *in vivo* using a rhesus macaque SARS-CoV-2 infection model (n=3 per group). Etesevimab at 50 mg/kg was administered intravenously 1 day prior (prophylaxis) or 1- and 3-days post exposure (therapeutic) to viral challenge. For the prophylaxis group, mean viral load was lower on Day 4 (by approximately $10^4$ RNA copies/mL), compared with the control group. X-ray and microscopic assessment of the lung indicated that administration of etesevimab reduced the severity of microscopic pulmonary changes induced by SARS-CoV-2, when compared with the lesions observed in the animals from the control group. In the treatment group, mean viral load was lower on Day 4 (by approximately $10^3$ RNA copies/mL), compared with control animals. Therapeutic administration of etesevimab reduced the severity of microscopic pulmonary changes induced by SARS-CoV-2, when compared with the lesions observed in the animals from the control group. The applicability of these findings to a prophylaxis or treatment setting is not known.

## 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.
  - The current supply of bamlanivimab includes (b) (4) vials that are packaged and labeled for immediate use. An additional (b) (4) vials will be available by end of February 2021.
  - The total projected supply by:
    - March is an additional (b) (4) (doses)
    - April 2021 is an additional (b) (4) vials
    - May 2021 is an additional (b) (4) vials
    - June 2021 is an additional (b) (4) vials
    - Q3 2021 is an additional (b) (4) vials

- Etesevimab is available in single use vials containing bamlanivimab 700 mg/20 mL per vial. Each dose requires two vials of etesevimab.
  - The current supply of etesevimab includes (b) (4) vials ((b) (4) doses) that are packaged and labeled for immediate use. An additional (b) (4) vials ((b) (4) doses) will be available by end of February 2021.
  - The total projected supply by:
    - March is an additional (b) (4) vials ((b) (4) doses)
    - May 2021 is an additional (b) (4) vials ((b) (4) doses)
    - June 2021 is an additional (b) (4) 0 vials ( doses)
    - Q3 2021 is an additional (b) (4) vials ( doses)
    - Q4 2021 is an additional (b) (4) vials ( doses)

## 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) mutations, 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 drug product with (b) (4) sensitivity. For the purpose of EUA, this test is sufficient to allow for timely delivery to the 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.

- 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 follows:

    - For bamlanivimab, 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 including 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 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 12-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 3 months at the long-term storage condition of 2°C to 8°C and 3 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 bamlanivimab and 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 INDs 150440 and 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

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

## XVI. Manufacturing Site Inspections

The following manufacturing and testing facilities are acceptable for etesevimab manufacture for the purpose of the EUA. Refer to EUA 000090 for facilities for bamlanivimab manufacture. Currently, bamlanivimab drug substance (DS) is manufactured at three manufacturing sites, including ImClone Systems LLC d.b.a. Eli Lilly Company, Branchburg, NJ (FEI 3002889358), (b) (4) ), and Eli Lilly Kinsale Ltd, Kinsale, Ireland (FEI 3002806888). Bamlanivimab DP is currently manufactured at four manufacturing sites, including Eli Lilly Company, Indianapolis (FEI 1819470), (b) (4) Lilly France, Fegersheim, France (FEI 3002807475) and (b) (4) . Control testing sites for bamlanivimab include (b) (4) and (b) (4) ). All sites, except ImClone Systems LLC (FEI 3002889358), have acceptable CGMP status. ImClone Systems LLC is under Official Action Indicated status; however, the risks associated with ImClone's manufacture of bamlanivimab DS under the EUA are sufficiently mitigated with specific required conditions of the authorization. Refer to OPQ EUA review memos for EUA000090 and OMQ memo (CMS case 611032 regarding Imclone) for additional

information on the manufacturing and testing sites. Additional DS and DP manufacturing sites are planned to be added. These sites will be evaluated at the time of submission. The Sponsor committed to obtain Agency concurrence prior to adding additional DS and DP manufacturing and testing facilities to the EUA. Product Quality reviews for EUA 90 are cross-referenced for detailed product quality data and information, including manufacturing facilities related to bamlanivimab.

**Table 26: Manufacturing Sites for Etesevimab for EUA 94**

| 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 | 05/25/2017 | Acceptable |
| (b) (4) | Drug Substance manufacturing and in-process/release testing | (b) (4) | IND 150707 | Eli Lilly and Company | (b) (4) | Acceptable* |
| 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 release/stability testing | (b) (4) | IND 150707 | Eli Lilly and Company | (b) (4) | Acceptable |
| | Adventitious virus testing of (b) (4) | | IND 150707 | Eli Lilly and Company | | Acceptable |
| | (b) (4) | | IND 150707 | Eli Lilly and Company | | Acceptable |

* 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 the writing of this review, no specific therapy is suggested for patients with COVID-19 who are not hospitalized in any of the following COVID-19 Treatment Guidelines:
    - The Centers for Disease Control (CDC) (https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html; updated December 4, 2020) notes that clinical management of COVID-19 includes infection prevention and control measures as well as supportive care, which includes hospitalization for supplemental oxygen and mechanical ventilatory support when indicated. Remdesivir has been approved for the treatment of COVID-19 in certain hospitalized patients. It is also noted that early effective treatment may help avert disease progression and that monoclonal antibodies are available under EUA for early outpatient treatment. It is stated that "clinicians and patients who wish to consider their use…should review the NIH COVID-19 Treatment guidelines as well as the FDA EUA for the therapy."
    - The Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 Infection (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management; updated November 18 2020) provides 15 recommendations related to the treatment of COVID-19. IDSA does not recommend any specific therapy for the treatment of patients with mild to moderate disease who are not hospitalized. While the IDSA guideline panel recommends against the routine use of bamlanivimab due to the low certainty of evidence, they note that bamlanivimab is a reasonable treatment option for patients at increased risk if, "after informed decision-making, the patient puts a high value on the uncertain benefits and a low value on uncertain adverse events."
    - The NIH COVID-19 Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/; updated December 3, 2020) reviews various treatments for COVID-19 and the associated available evidence. No specific antiviral or immunomodulatory therapy is recommended for patients who are not hospitalized or are hospitalized but do not require supplemental oxygen. It is noted that while there are insufficient data from clinical trials to recommend either for or against the use of any specific monoclonal antibody against SARS-CoV-2, preliminary data suggests that outpatients may benefit from receiving anti-SARS-CoV-2 monoclonal antibodies early in the course of infection. The panel supports the use of other agents, such as remdesivir and dexamethasone, for later stages of illness, particularly in

patients who are are hospitalized and require supplemental oxygen or other higher levels of care.

## 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. Bamlanivimab and etesevimab have demonstrated activity in cell culture and in animal models against SARS-CoV-2, and are currently being evaluated in clinical trials for both prophylaxis and treatment indications.

Based on review of data from Trial J2W-MC-PYAB, also called BLAZE-1 (NCT04427501), a randomized, double-blind, placebo-controlled, phase 2/3 trial in outpatients with mild to moderate COVID-19, it is reasonable to believe that bamlanivimab and etesevimab administered together "may be effective" 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. The known and potential benefits of bamlanivimab and etesevimab administered together outweigh the known and potential risks of the drugs for the proposed authorized use.

The primary endpoint for Treatment Arms 7-8 in Trial PYAB was COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause through Day 29. Event rates for the primary analysis were 7% for the placebo group versus 2% for the treatment group, which was highly statistically significant and corresponded to an estimated number needed to treat of 21 high risk outpatients to prevent 1 hospitalization or death event. There was also a nominally significant difference in all-cause mortality alone through Day 29 with 10 deaths in the placebo arm and no deaths in the treatment arm. Key secondary virologic and symptoms endpoints also all significantly favored bamlanivimab 2800 mg and etesevimab 2800 mg administered together compared with placebo. Data from the phase 3 portion of this trial therefore provides persuasive evidence of benefit, not only to individual patients, but could also ameliorate the significant burden that the COVID-19 pandemic has placed on the public health system.

The phase 2 data from Trial PYAB Treatment Arms 1-4 and 6 were also supportive of efficacy and informed dosing. The primary endpoint was change from baseline of SARS-CoV-2 viral load at Day 11. Compared with placebo, viral load was lower in patients treated bamlanivimab 2800 mg and etesevimab 2800 mg by a statistically significant degree. The predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits also favored bamlanivimab and etesevimab

compared with placebo. Participants in Treatment Arms 2-4 were treated with bamlanivimab alone at doses of 700 mg, 2800 mg, and 7000 mg. Results in these groups also favored bamlanivimab compared with placebo for COVID-19-related hospitalizations or emergency room visits and for symptom burden through Day 11. Furthermore, these clinical efficacy data did not show a dose-response relationship for bamlanivimab when given alone, which supported use of the 700 mg dose.

The clinical outcomes data supporting the authorization of bamlanivimab and etesevimab administered together were generated from the phase 2 and 3 portions of Trial PYAB (BLAZE-1), where patients received bamlanivimab 2800 mg and etesevimab 2800 mg. The authorized dose of bamlanivimab 700 mg and etesevimab 1,400 mg, in addition to bamlanivimab 2,800 mg and etesevimab 2,800 mg, was studied in another randomized, double-blind, placebo-controlled clinical trial (BLAZE-4) in subjects with mild to moderate COVID-19, with and without risk factors for progression of COVID-19 disease. For the primary endpoint of persistently high viral load at Day 7 (+2), both bamlanivimab 700 mg and etesevimab 1400 mg and bamlanivimab 2800 mg and etesevimab 2800 mg treatment were superior to placebo; differences between bamlanivimab 700 mg and etesevimab 1400 mg and bamlanivimab 2800 mg and etesevimab 2800 mg were consistent with chance variation. Moreover, point estimates for average changes from baseline in SARS-CoV-2 viral load were higher for bamlanivimab 700 mg and etesevimab 1400 mg than for bamlanivimab 2800 mg and etesevimab 2800 mg for the secondary endpoints at Days 3, 5, and 7. Therefore, virologic data from the phase 2 trial PYAH support bamlanivimab 700 mg and etesevimab 1400 mg as the authorized dosage. Based on these clinical and virologic data, as well as supportive pharmacokinetic/pharmacodynamic modeling, the authorized dosage of 700 mg bamlanivimab and 1,400 mg etesevimab is expected to have similar clinical effect to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab.

Regarding assessment of the known and potential risks, the overall safety database of bamlanivimab is comprised of more than 1500 COVID-19 patients who have received an IV infusion of bamlanivimab and etesevimab at the authorized dose or higher. In addition, over 3900 patients have received bamlanivimab (alone or with etesevimab) at doses ranging from 700 to 7000 mg during the clinical development program. The major adverse events of concern were hypersensitivity and infusion reactions, though serious infusion reactions and anaphylaxis were rare. Generally, most infusion reactions were reported as mild or moderate in Trial PYAB. 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.

Although not evaluated in clinical trials, a potential benefit of using bamlanivimab and etesevimab together is to reduce the potential risk of treatment failure should a patient be infected with a SARS-CoV-2 viral variant that is resistant to bamlanivimab alone. Indeed, new variants have been identified within the United States and in other countries and it is possible that other variants may emerge in the future. Based on pseudovirus data, it is likely that bamlanivimab and etesevimab retain neutralizing activity against variants harboring spike protein substitutions identified in isolate B.1.1.7 (UK origin) but likely have reduced activity against variants harboring spike protein substitutions identified in isolate B.1.351 (South African origin). The Applicant is still conducting studies to determine if bamlanivimab or etesevimab have neutralizing activity against authentic SARS-CoV-2 variants. 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 or bamlanivimab and etesevimab together should be made in the context of what is known about local prevalence of these variants at the time of treatment.

Treatment emergent resistant variants were less frequently detected in patients who received bamlanivimab and etesevimab together compared to patients who received bamlanivimab alone or received placebo in Treatment Arms 1-4 and 6 of Trial PYAB. Because the emergence of resistant variants is still a potential risk, treated patients 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 in order minimize the spread of SARS-CoV-2. It is reasonable to believe that a combination of two monoclonal antibodies would be less likely to be associated with this risk of the emergence of viral variants.

Bamlanivimab and etesevimab have not been studied in patients hospitalized due to COVID-19. Given this, and that the use of monoclonal antibodies such as these products may be associated with risk of worse clinical outcomes in patients with severe COVID-19, bamlanivimab and etesevimab will not be authorized for 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 individuals with an underlying non-COVID-19 related comorbidity that requires chronic oxygen therapy.

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 the totality of the scientific information available, including clinical efficacy and safety, virologic data and resistance information, and PK/PD data, it is reasonable to believe that the authorized dose of bamlanivimab 700 mg and etesevimab 1400 mg administered together “may be effective” for the proposed authorized use and the known and potential benefits of bamlanivimab and etesevimab for the authorized use outweigh the known and potential risks. Therefore, the Review Division and the Office of Infectious Diseases recommends authorization of an EUA for bamlanivimab 700 mg and etesevimab 1400 mg 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 progressing to severe COVID-19 and/or hospitalization.

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

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

EUA-labled 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 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 either 100 or 140 cartons. By the end of Q1, the packaging will be changed so that all cases will contain 100 cartons. Each carton contains one vial of bamlanivimab 700 mg or one vial of etesevimab 700 mg and a leaflet with the QR code and the global URL www.BAMandETE.com
    - Hard copies of the fact sheets will not be included but can be printed from the QR code or Global URL.
- The Global URL will allow users to be directed to the US URL www.bamlanivimabBAMandETE.comThe following ULR is included on the label and carton of bamlanivimab: www.bamlanivimabHCPinfo.com
- The following ULR is included on the label and carton of etesevimab: 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 for www.BAMandETE.com

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

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

- Fact Sheet for Patients, Parents and Caregivers (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. Pharmacometric PK/PD Review of Dose Selection
2. Fact Sheet for Health Care Providers
3. Fact Sheet for Patients and Parent and Caregivers

# Appendix 1. Pharmacometric PK/PD Review of Dose Selection

## Executive Summary

Bamlanivimab and etesevimab are both recombinant neutralizing human IgG1κ mAbs to the spike protein on SARS-COV-2. The proposed dosing regimen for EUA94 is a single dose of 700 mg bamlanivimab and 1400 mg etesevimab administered together via intravenous infusion. Evidence that bamlanivimab "may be effective" for the treatment of COVID-19 was evaluated in the EUA90 application, and the 700 mg dose was accepted based on the totality of the scientific evidence related to virology, symptomology, and hospitalization. To date, the only available clinical data from patients receiving 700 mg bamlanivimab and 1400 mg etesevimab administered together is virology data from Study PYAH without clinical outcomes (see Section VIII). This review aims to evaluate this proposed dosing regimen based on the totality of the available clinical and in vitro data and viral dynamics model.

In Study PYAH, a dosage of 700 mg bamlanivimab and 1400 mg etesevimab administered together produced similar antiviral activity to a dosage of 2800 mg bamlanivimab and 2800 mg etesevimab administered together. In Study PYAB, the combination of 2800 mg bamlanivimab and 2800 mg etesevimab reduced viral load and hospitalizations relative to placebo for virology, symptomology, or reduction in hospitalizations or emergency room visits. In addition, bamlanivimab and etesevimab administered together resulted in fewer treatment-emergent variants and an additional reduction in viral load relative to bamlanivimab alone. For the combination therapy, to provide coverage of the different but overlapping epitopes on SARS-CoV-2 receptor binding domain sites for bamlanivimab and etesevimab, the dose selection rationale for each mAb in the combination is the same as the dose rationale for a single mAb. PK/PD modeling has been used to estimate the *in vivo* $EC_{90}$ value for etesevimab, which predicted a minimum of 11-fold margin between serum concentrations and the $EC_{90}$ value for 28 days. Therefore, 1400 mg etesevimab when administered with 700 mg bamlanivimab was anticipated to achieve comparable efficacy to the aforementioned combination dosage evaluated in Study PYAB (2800 mg). The comparable anti-viral effect between the two doses was confirmed in Study PYAH.

We conclude the PK/PD model adequately describes the data. Our independent sensitivity analysis indicates that the proposed dose after intravenous infusion is expected to provide a sufficient margin of serum concentrations over *in vivo* $EC_{90}$ value up to 28 days.

# Summary of Clinical Pharmacology Assessment

## *1. Clinical Pharmacokinetics*

The summary of general pharmacology and pharmacokinetic characteristics of bamlanivimab and etesevimab is provided in **Table 27**. 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.

The PK of bamlanivimab and etesevimab were not affected by age (18 to 86 years of age), sex, race, disease severity (moderate/severe in PYAA [bamlanivimab] vs. mild/moderate in PYAB [bamlanivimab and etesevimab]) or baseline viral load based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bamlanivimab in adults with COVID-19 over the body weight range of 41 to 173 kg.

## *2. General Dosing and Therapeutic Individualization*

The authorized dosage for bamlanivimab and etesevimab for adults and pediatric patients (12 years of age and older, who weigh weighing ≥40 kg) is a single intravenous infusion of 700 mg bamlanivimab and 1400 mg etesevimab.

No dose adjustment is recommended based on age (18 to 86 years of age), sex, race, or disease severity, body weight (41 to 173 kg), renal impairment, and mild hepatic impairment. No dosage adjustment is recommended for pregnant or lactating patients. Bamlanivimab and etesevimab has not been studied in pregnant or lactating women.

Bamlanivimab and etesevimab are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, no dose adjustment is recommended for concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes.

**Table 27. Summary of general pharmacology and pharmacokinetic characteristics of bamlanivimab and etesevimab**

| **Pharmacology** | | | |
|---|---|---|---|
| **Mechanism of Action** | | Bamlanivimab and etesevimab are recombinant neutralizing human IgG1κ mAbs to the spike protein of SARS-CoV-2.Bamlanivimab and etesevimab bind to the spike protein RBD with $K_D$ = 2.2 nM and 6.45 nM, respectively, block interaction between human ACE2 receptor and spike protein RBD with $IC_{50}$ values = 0.17 nM and 0.32nM, respectively. | |
| **General Information** | | | |
| **Dose Proportionality** | | Linear PK from 700-7000 mg with intravenous infusion. | |
| **Disposition** | | **Bamlanivimab** | **Etesevimab** |
| **Absorption** | Maximum concentration | $C_{max}$ was 196 µg/mL (90% CI: 102 to 378 µg/mL) following ~1 h 700 mg IV infusion. | $C_{max}$ is estimated 504 µg/mL (90% CI: 262 to 974 µg/mL) following ~1 h 1400 mg IV infusion. |
| **Distribution** | Volume of Distribution | $V_{ss}$ is 6.47 L (CV%=24.8%) | $V_{ss}$ is 4.86 L (CV%=25.2%) |
| **Metabolism** | Primary Metabolic Pathway(s) | 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** | Clearance | CL is 0.307 L/d (CV%=26%) | CL is 0.142 L/d (CV%=31.6%) |
| | Terminal Phase Half-Life | $t_{1/2}$ is 17.6 d (CV%=15.8%) | $t_{1/2}$ is 25.1 d (CV%=29.2%) |
| **Interaction liability (Drug as Perpetrator)** | | | |
| **Inhibition/Induction of Metabolism and Transporter Systems.** | | 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. | |

# Key Questions

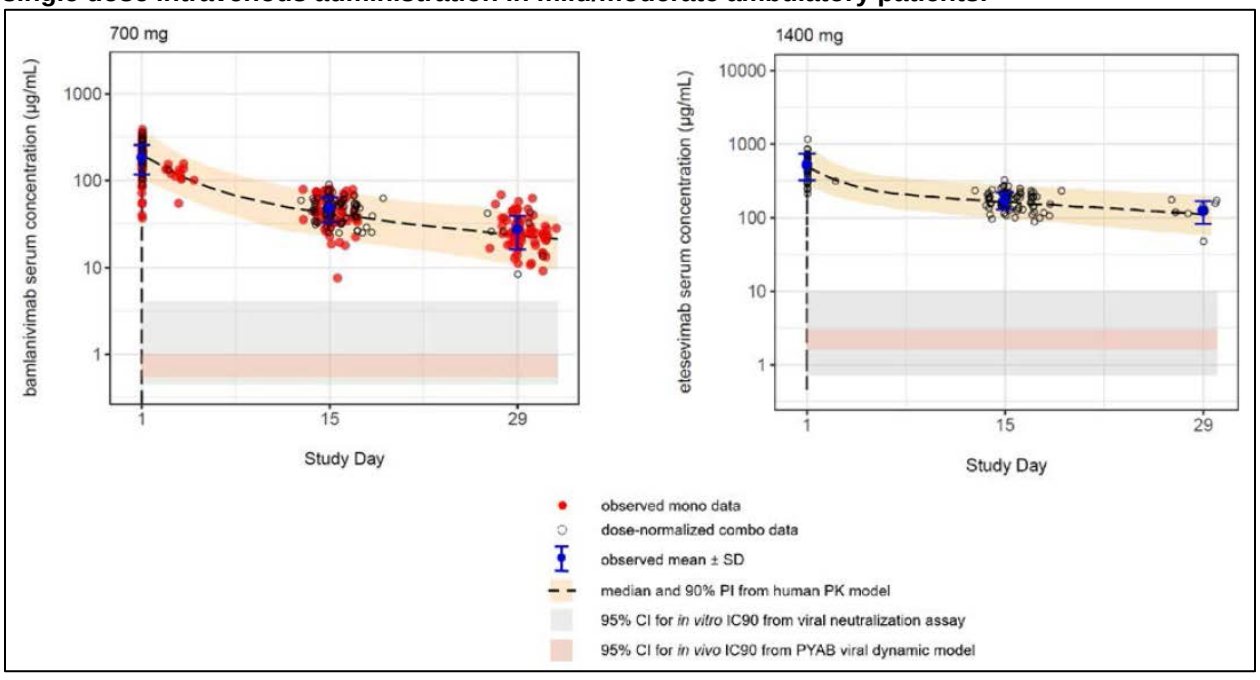
## *1. Does the available PK and PD data support the recommended dosing regimen?*

Yes.

The 700 mg bamlanivimab dose achieved serum concentrations above the *in vivo* EC90 value of viral load reduction for at least 28 days in 90% of the patient population (**Figure 5**). The *in vivo* EC90 of etesevimab is expected to be no more than 8-fold higher than that of bamlanivamab based on comparison of the in vitro $EC_{90}$ values of bamlanivimab and etesevimab and population PK-PD modeling. Therefore, the 1400 mg etesevimab dose achieved serum concentrations above the expected *in vivo* $EC_{90}$ value of viral load reduction for at least 28 days in 90% of the patient population (**Figure 5**). Given at least 11× margin of serum concentration over $EC_{90}$ value on day 29, the proposed dose of bamlanivimab and etesevimab is expected to provide near-maximal antiviral activity (see the **Reviewer's Independent Analysis** for further details). Available clinical data demonstrate that a dosage of 700 mg bamlanivimab and 1,400 mg etesevimab administered together has similar antiviral activity to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab administered together. Refer to Section VIII and XI for further details.

The viral reduction in the high-risk patients was estimated to be ~60% of the low-risk patients. The proposed dose of bamlanivimab and etesevimab is expected to achieve near-maximal efficacy irrespective of risk strata.

**Figure 5. PK profiles of 700 mg bamlanivimab (left) and 1400 mg etesevimab (right) after single dose intravenous administration in mild/moderate ambulatory patients.**



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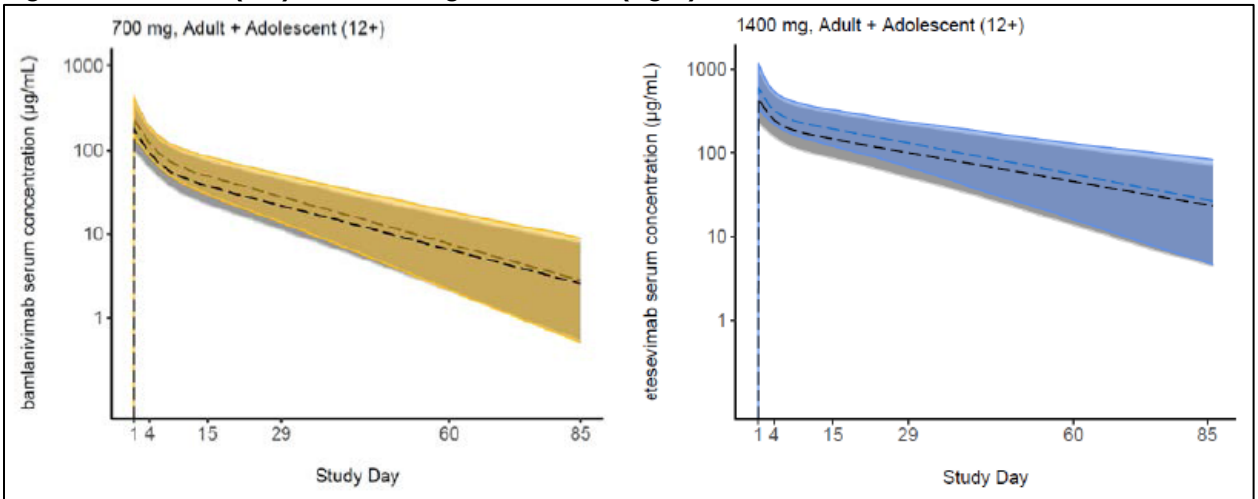
## *2. Is the proposed dose appropriate for pediatric patients age 12 years of age or older?*

Yes.

The combination therapy is extended to adolescents aged 12 years of age or older who weigh at least 40 kg and are considered high-risk under this EUA. Efficacy of bamlanivimab and etesevimab has not been evaluated in this population, therefore the dose for adolescents was proposed based on exposure-matching approach. The PK of bamlanivimab and etesevimab have only been studied in adults (weight range: 41-173 kg). Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after accounting for the effect of body size on PK. Using modeling and simulation, the authorized dosing regimen is expected to result in comparable plasma exposures of bamlanivimab and etesevimab in pediatric patients aged 12 years of age or older who weigh at least 40 kg as observed in adult patients (**Figure 6**). The median AUC in pediatrics is approximately 25% higher than that in adults. Based on the available safety data of bamlanivimab and etesevimab including those from higher dose cohorts, the proposed dose for pediatrics is acceptable.

**Figure 6. PK profile in pediatric patients ≥40 kg body weight is similar to adults after 700 mg bamlanivimab (left) and 1400 mg etesevimab (right).**




The grey lines and regions are the median and 90% PI of PK model-predicted adult profile following 700 mg bamlanivimab IV (left) or 1400 mg etesevimab IV (right). The gold (bamlanivimab) and blue (etesevimab) lines and regions are the median and 90% PI of the simulated pediatric profiles at the proposed doses.

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# Population PK/PD Review

## *1. Population PK Analysis*

### 1.1 Overview of studies included in population PK analysis

The applicant conducted a population PK analysis to characterize the PK of bamlanivimab and etesevimab, identified covariate factors that could affect disposition, and exported the individual exposure estimates for subsequent viral dynamic analysis. PK and PD analyses included the studies listed in **Table 28**.

**Table 28. Clinical studies used in PK/PD analysis (Nov, 2020).**

| Study | Description and Number used in PK/PD | Dose and Sampling Time |
|---|---|---|
| PYAA | Phase 1, randomized, placebo-controlled, single ascending dose trial in hospitalized adults with moderate or severe COVID-19. (n=18 for bamlanivimab PK) | Single IV dose 700 mg, 2800 mg, or 7000 mg of bamlanivimab.<br>PK sampling: Day 1, 4, 15, 29. |
| PYAB | Phase 2/3, randomized, placebo-controlled trial in ambulatory adults with mild to moderate COVID-19 illness. (n=396 for bamlanivimab PK, n= 93 for etesevimab PK, n= 571 for PD analysis and symptom analysis) | • Single IV dose 700 mg, 2800 mg, or 7000 mg of bamlanivimab.<br>• Single IV dose 2800 mg bamlanivimab + 2800 mg etesevimab.<br>PK sampling: Day 1, 15, 29, 60, 85.<br>PD NP swab: Day 1, 3, 7, 11, 15, 18, 22, 25, 29, 60<br>Symptoms: Daily on Days 1-29 |
| PGAA | Phase 1, randomized, placebo-controlled trial in healthy participants. (n=20 for etesevimab PK) | Single IV dose 700 mg, 2800 mg, or 7000 mg of etesevimab.<br>PK sampling: Day 1, 2, 3, 8, 15, 29, 43, 57, 85. |

### 1.2 Population PK modeling

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.4.2 using first-order conditional estimation with INTERACTION option (FOCE+I). Concentrations collected before the first dose were excluded from the PK analysis as well as post-dose observations that were below the limit of quantification (BLQ).

Baseline patient characteristics of the population PK dataset of bamlanivimab and etesevimab are summarized in **Table 29** and **Table 30**, respectively. For bamlanivimab, a total of 977 samples from 18 hospitalized patients (PYAA) and 396 ambulatory patients (PYAB) were included for the population PK analysis. For etesevimab, a total of 330 samples from 20 health adults (PGAA) and 93 ambulatory patients (PYAB) were included for the population PK analysis. Covariates explored included age, body weight, sex, race, baseline viral load, study/population, dose, hepatic impairment, coadministration with bamlanivimab or etesevimab.

The final population PK parameters for bamlanivimab and etesevimab are presented in the **Table 31** and **Table 32**, respectively. The final PK models were all parameterized in terms of CL, V1, Q, and V2. No covariates except weight were clinically and statistically significant.

**Table 29. Patient characteristics in bamlanivimab PK analysis dataset.**

| | Median | Minimum | Maximum | Not Reported |
|---|---|---|---|---|
| Weight (kg) | 82.9 | 41.6 | 173 | 24 |
| Age (y) | 45 | 18 | 86 | |
| Baseline Viral Load [(40-cycle time)/log2(10)] | 5.30 | 0 | 8.66 | 9 |
| Sex (%) | Female | Male | | |
| | 54.8 | 45.2 | | |
| Race (%) | White | Black or African American | Asian | All Others[a] |
| | 87.9 | 6.5 | 2.9 | 2.7 |
| Hepatic Status (%) | Normal | Mild | Not Reported | |
| | 74.2 | 21.0 | 4.8 | |

Abbreviation: PK = pharmacokinetics.

[a] American Indian or Alaska native; Native Hawaiian or other Pacific Islander; Multiple; Not Reported.

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**Table 30. Patient Characteristics in Etesevimab PK Analysis Dataset.**

| | Median | Minimum | Maximum | Not Reported |
|---|---|---|---|---|
| Weight (kg) | 77.5 | 41.4 | 173 | 3 |
| Age (y) | 42 | 19 | 76 | |
| Sex (%) | Female | Male | | |
| | 46.0 | 54.0 | | |
| Race (%) | White | Black or African American | Asian | Not Reported |
| | 90.3 | 5.31 | 3.54 | 0.88 |
| Hepatic Status (%) | Normal | Mild | Not Reported | |
| | 81.4 | 13.3 | 5.31 | |

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**Table 31. Population pharmacokinetic model parameters for bamlanivimab.**

| Parameter Description | Population Estimate (%SEE) | Interpatient Variability (%SEE) |
|---|---|---|
| CL (L/d) | 0.270 (2.77) | 22.3 (18.7) |
| Q (L/d) | 0.375 (22.1) | -- |
| Effect[a] of body weight on CL and Q | 0.81 (Fixed) | -- |
| V1 (L) | 2.87 (2.12) | 23.2 (31.6) |
| V2 (L) | 2.71 (6.13) | -- |
| Effect[b] of body weight on V1 and V2 | 1.00 (Fixed) | -- |
| Residual Error (proportional) | 20.6% (8.88) | |

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**Table 32. Population pharmacokinetic model parameters for etesevimab.**

| Parameter Description | Population Estimate (%SEE) | Interpatient Variability (%SEE) |
|---|---|---|
| CL (L/d) | 0.128 (4.08) | 33.8 (19.0) |
| Q (L/d) | 0.514 (7.04) | -- |
| Effect[a] of body weight on CL and Q | 0.81 (Fixed) | -- |
| V1 (L) | 2.38 (3.52) | 27.8 (43.9) |
| V2 (L) | 1.98 (3.20) | -- |
| Effect[b] of body weight on V1 and V2 | 1.00 (Fixed) | -- |
| Residual Error[c] | | |
| Additive (µg/mL) | 8.40 (30.8) | |
| Proportional | 8.45% (21.8) | |

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Estimated fixed and random effect parameters were estimated with good precision (%RSE < 30%) with the exception of V1 for both antibodies. The magnitude of the interindividual variability was <30% CV except CL for etesevimab which was 33.8%. Residual variability was small (see **Table 31**and **Table 32** above).

The diagnostic plots showed no obvious bias in prediction relative to observations across the entire concentration or time range (**Figure 7** and **8**). Visual predictive check for the final PK models were stratified by dose (**Figure 9** and **10**). Overall, the model described the data reasonably well.

**Figure 7. Goodness-of-fit for bamlanivimab population PK model.**

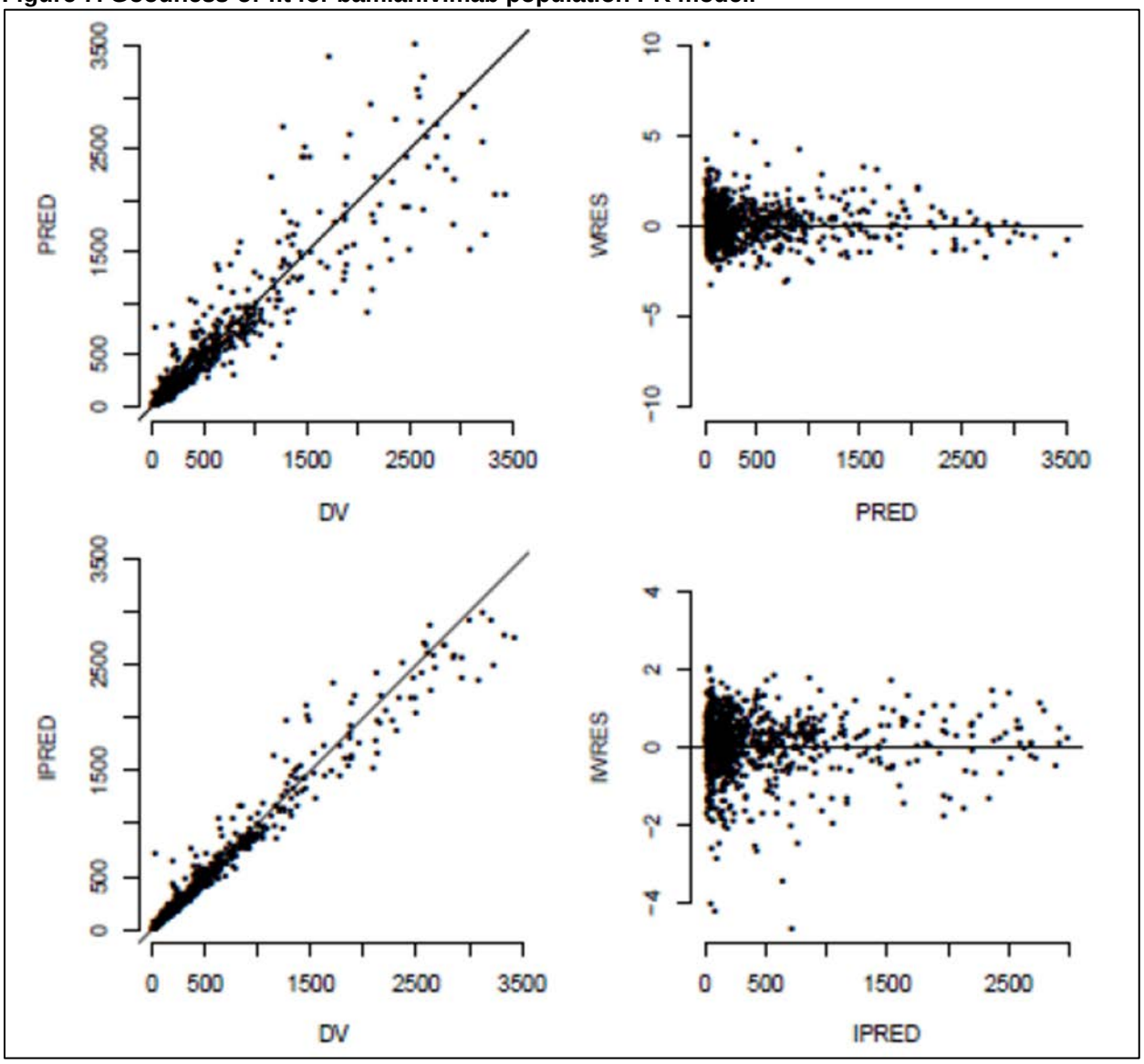


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**Figure 8. Goodness-of-fit for etesevimab population PK model.**

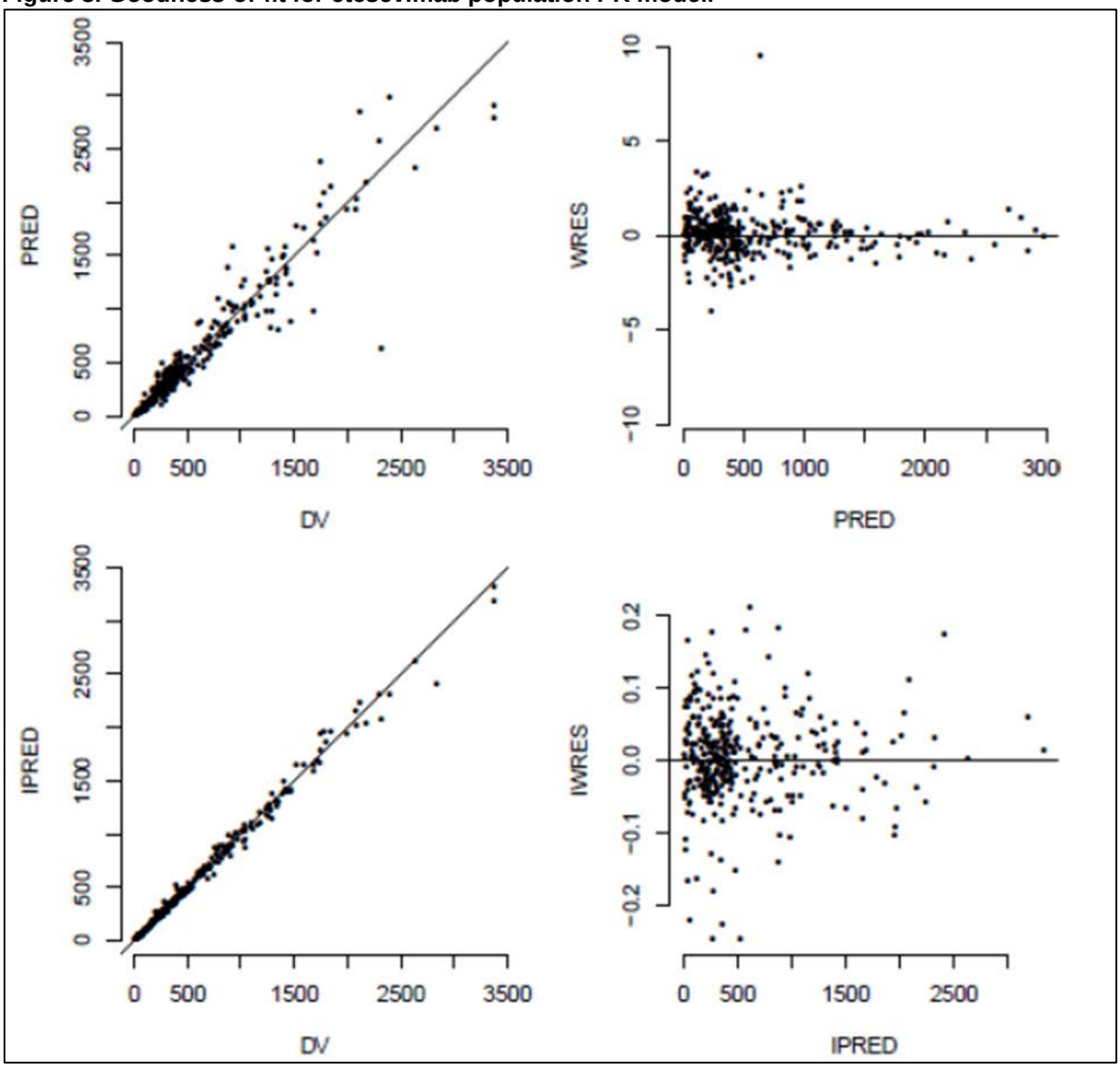


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**Figure 9. Visual predictive check for bamlanivimab population PK model.**

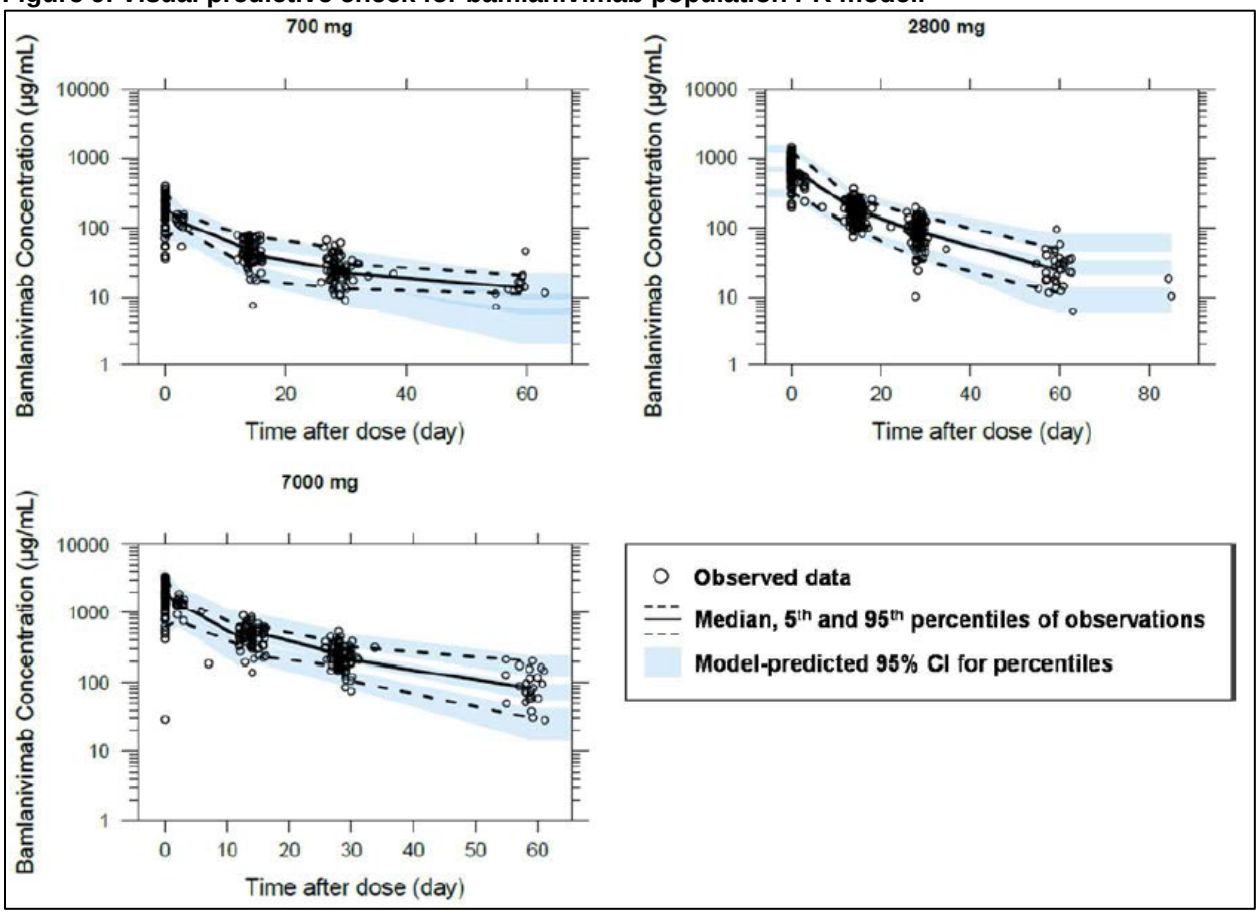


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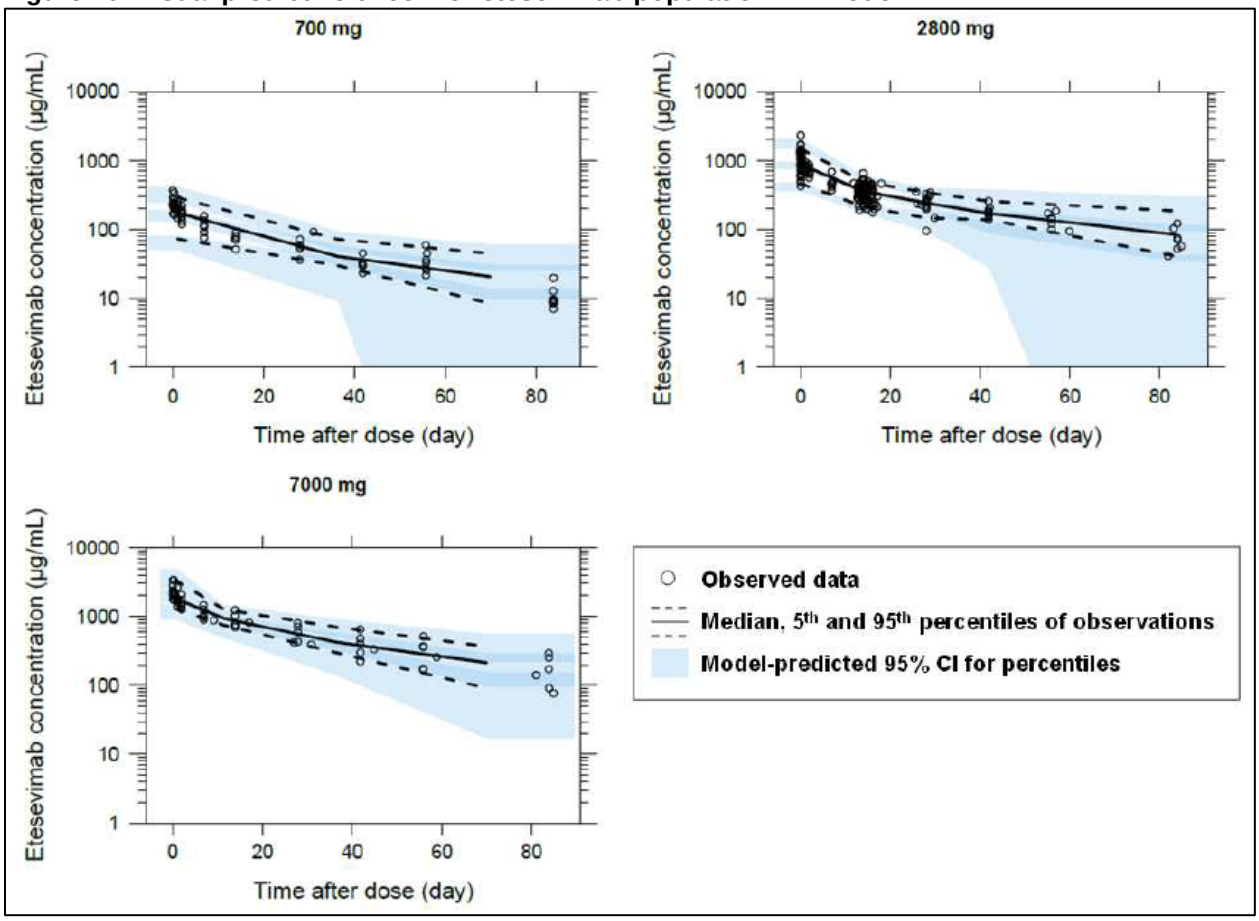
**Figure 10. Visual predictive check for etesevimab population PK model.**

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## 1.3 Technical review

1.3.1 Observed underprediction in VPC of bamlanivimab is likely due to BLQ.
The median of the 5th percentile of observations was found to be above the 95% CI ribbon for 5th percentile simulated concentrations with 700 mg dose on day 60, suggesting an underprediction of the model for low concentrations. The underprediction is likely not true given some BLQ observations on day 60 (LOQ = 5 or 10 µg/mL).

The number of BLQ measurements determined on days 29, 60, and 85 of bamlanivimab treatment was summarized in **Table 33.** Apart from that, 9 BLQ were collected before the end of infusion. One BLQ on day 16 with 2800mg bamlanivimab dose [ID=(b) (6)] was unlikely, but CSR of PYAB is not available to check for protocol deviation. One BLQ measurement indicated for day 29 visit was collected on day 46 [ID=(b) (6)] and hence was not included in the table. In summary, >99% of samples in bamlanivimab treated subjects were quantifiable up to day 29. All samples in etesevimab treated subjects were quantifiable up to day

85 except for 2 samples (one collected before the end of infusion, one on day 16 after a 2800 mg dose [ID= (b) (6) ] which needs to be verified with CSR).

The M3 and M4 methods of handling BLQ measurements were utilized to evaluate the accuracy of the parameter estimates. Overall, the parameter estimates were not greatly affected by the number of BLQ observations that accounted for 20.2% of all observations (including 25 measurable observations with 7000 mg dose) on day 60 **(Table 34).**

**Table 33. Number of BLQ with bamlanivimab treatment on days 29, 60, and 85.**

| Dose | Day 29 | | | Day 60 | | | Day 85 | | |
|---|---|---|---|---|---|---|---|---|---|
| | BLQ | Total | % | BLQ | Total | % | BLQ | Total | % |
| 700 mg | 2 | 81 | 2.7 | 17 | 29 | 58.6 | 7 | 7 | 100 |
| 2800 mg | 0 | 92 | 0 | 1 | 35 | 2.9 | 3 | 5 | 60 |

Table summarized based on data from meta_pk_2020-11-03.csv.

**Table 34. Comparison of PK parameter estimates using M3 and M4 method for BLQ.**

| PK parameter estimates | Applicant's model | M3 method | | M4 method | |
|---|---|---|---|---|---|
| | | Value | Bias | Value | Bias |
| CL (L/d) | 0.27 | 0.269 | -0.4% | 0.268 | -0.7% |
| V1 (L) | 2.87 | 2.75 | -4.2% | 2.76 | -3.8% |
| Q (L/d) | 0.375 | 0.479 | 27.7% | 0.459 | 22.4% |
| V2 (L) | 2.71 | 2.91 | 7.4% | 2.87 | 5.9% |
| IIV-CL (%CV) | 22.3% | 19.5% | -12.5% | 19.5% | -12.5% |
| IIV-V1 (%CV) | 23.2% | 18.6% | -19.8% | 19% | -18.1% |
| Prop error (%CV) | 20.6% | 24.9% | 20.9% | 24.7% | 19.9% |

1.3.2 Exponent of weight allometry

For the population PK analysis of bamlanivimab and etesevimab, the effect of body weight was included as a power function with fixed exponents of 0.81 for clearance (CL, Q) and 1 for volume (V1, V2). Based on weight allometry with the exponent of 0.81, the CL is estimated to be 77.2% and 169% of the population CL estimate for the 2.5th and 97.5th weight percentiles. To examine if the fixed exponents were appropriate, the reviewer estimated the exponents to compare with the fixed value. For bamlanivimab, the estimated exponents were 0.713 for clearance and 0.609 for volume, reducing the IIV of V1 by 2.1%CV. For etesevimab, the estimated exponents were 0.705 for clearance, and 0.611 for volume, reducing the IIV of V1 by 2.2%CV. Therefore, the difference was not considered significant based on the criteria defined in the method (a ≥5% reduction in interindividual variability (as %CV [percent coefficient of variation]) in the relevant bamlanivimab or etesevimab parameter). The appropriateness of applying the fixed weight allometry for dose extrapolation in pediatric patients under 40 kg needs to be further assessed.

Reviewer comments:
The PK model appropriately described the observed data. The data are thus acceptable for PK/PD modeling and the HCP factsheet. Over 99% of concentrations were quantifiable up to day 29 for reliable estimation of PK parameters in the two-compartment models. Small discrepancies were identified with implementation of M3/M4 method for BLQ or using unfixed weight exponents, neither of which were likely to be clinically significant.

## *2. PK/PD Analysis*

### 2.1 Overview of studies included in the E-R analysis

Efficacy data from the PYAB study was utilized for the E-R efficacy analyses of viral load reduction and symptomology (see **Table 28**). The PK/PD analysis was conducted via NONMEM software, version 7.4.2 using sequential ITS, SAEM, and IMP.

PK/PD model included the following:

- Target-cell limited viral dynamic model for viral reduction
- Multinomial logistic regression model for symptomology which includes the following 8 key symptoms: body aches and pain (BAP), chills, cough, fatigue, fever, headache, shortness of breath (SOB), and sore throat (STHRT).

### 2.2 Viral dynamic model

To provide evidence-based support for the proposed dose of bamlanivimab and etesevimab, in particular 1400 mg etesevimab that has not been clinically evaluated, a PK/PD analysis for viral load reduction was carried out to estimate the serum concentrations of bamlanivimab and etesevimab that were expected to achieve 90% of anti-viral effect ($EC_{90}$) *in vivo*.

A total of 4546 observations from 571 ambulatory patients (PYAB) were included in the PK/PD analysis. The breakdown of the data for each study group is summarized in **Table 35**. Covariates explored were age, body weight, body mass index, high-risk status, and the granular high-risk factors including medical history of immune disorders (including diabetes), chronic kidney disease, concomitant immunosuppressive medications, and age >55 with underlying disease (i.e. cardiovascular disease, hypertension, or chronic obstructive pulmonary disease).

**Table 35. Patients Included in PK/PD Analysis.**

| Study group | Placebo | Monotherapy (Bamlanivimab) | | | Combination Therapy |
|---|---|---|---|---|---|
| | | 700 mg | 2800 mg | 7000 mg | 2800 mg each |

| | | | | | |
|---|---|---|---|---|---|
| # of patients/observations | 152/1184 | 101/829 | 107/880 | 100/821 | 111/832 |

A target-cell limited, viral-dynamic model based on Baccam et al. 2006 (**Figure 11**) was used to describe the reduction of viral load over time as a function of natural decline and drug effect. A non-linear sigmoidal $E_{max}$ model was used to model the drug action on viral clearance. The Hill coefficient was fixed to 4 for both bamlanivimab and etesevimab. The drug effect on viral clearance is as follows:

- For bamlanivimab monotherapy

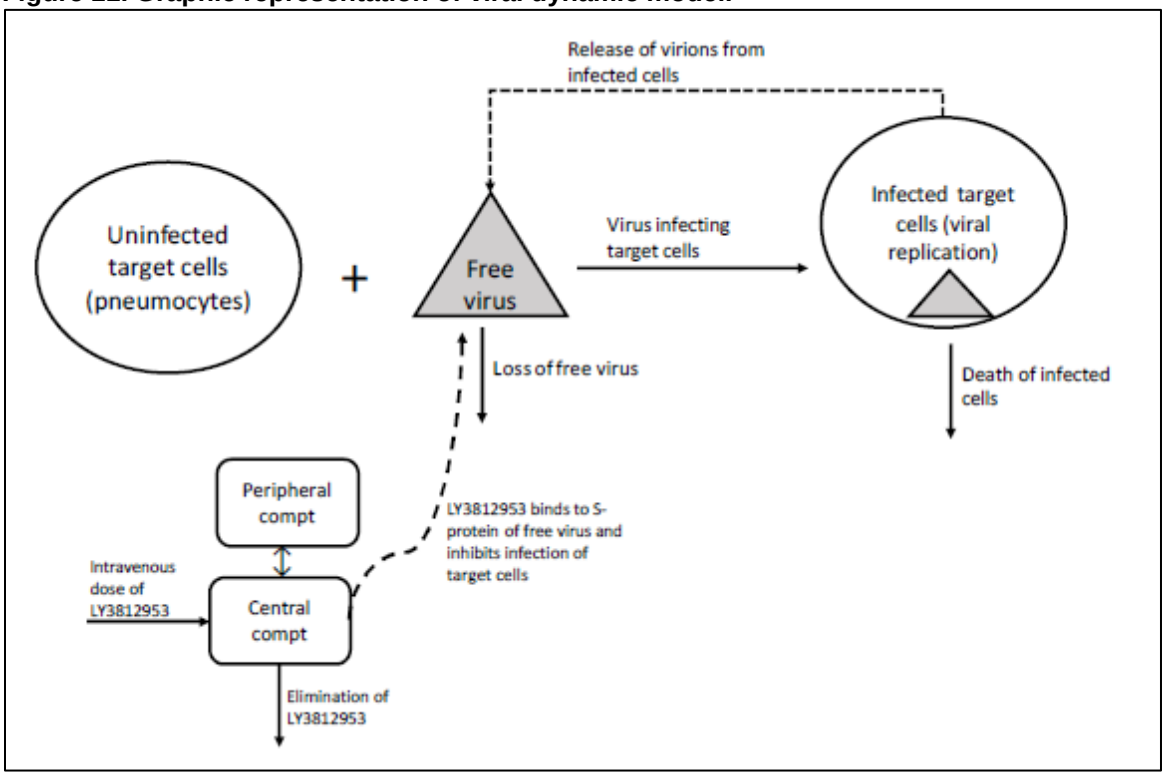
$$CVt = CV * (1 + \frac{E_{max} \times conc^{hill}}{EC_{50}{}^{hill} + conc^{hill}})$$

- For bamlanivimab and etesevimab combination therapy

$$CVt = CV + \frac{E_{max} \times conc1^{hill}}{EC_{50}{}^{hill} + conc1^{hill}} + \frac{E_{max} \times conc2^{hill}}{(EC_{50}{}^{hill} \times 3) + conc2^{hill}}$$

Where CV is the natural elimination rate of virus; conc1 is the serum concentration of bamlanivimab; conc2 is the serum concentration of etesevimab; $EC_{50}$ value of etesevimab is assumed to be 3 times the $EC_{50}$ value of bamlanivimab; hill is the hill coefficient (fixed to 4). $EC_{90}$ can be calculated from $EC_{50}$ using the formula: $EC_{90} = 9^{1/Hill} \times EC_{50}$.

**Figure 11. Graphic representation of viral dynamic model.**



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The fixed and random effect parameters were estimated with good precision (%RSE < 30%) except for $EC_{50}$ (%RSE=35.3%) and fractional decrease in Emax for high-risk patient (%RSE=31.8%). The magnitude of the interindividual variability was fixed to 15%CV. The correlations between the random effects of infection rate constant, viral production rate, and viral elimination rate were moderate to high. Residual variability was large (additive error of 0.874 for log viral load).

The diagnostic plots showed underprediction for observations of low viral load which appeared to start at day 15 of treatment initiation (**Figure 12**). This is likely due to the LOQ of viral detection. Visual predictive check for the final viral dynamic models were stratified by dose and risk strata (**Figure 13**). Overall, the model described the individual data reasonably well.

**Figure 12. Goodness-of-fit plots for viral dynamic model.**

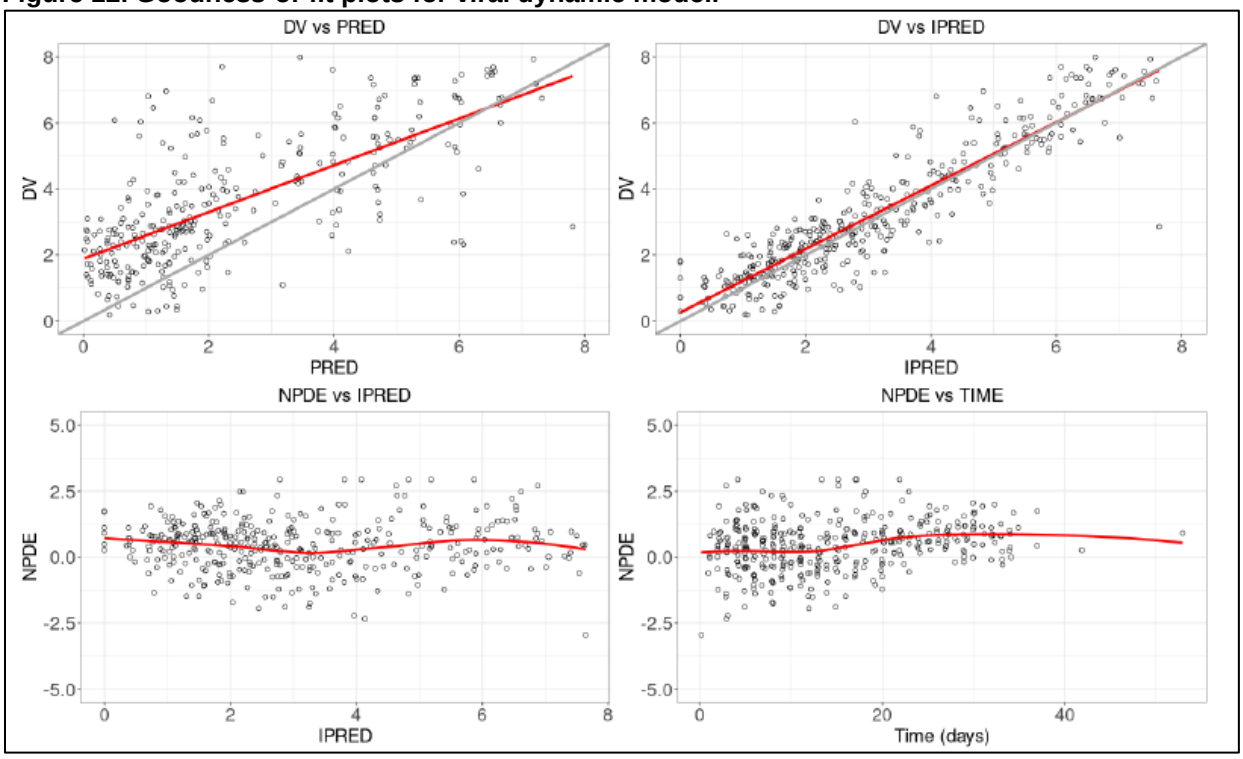
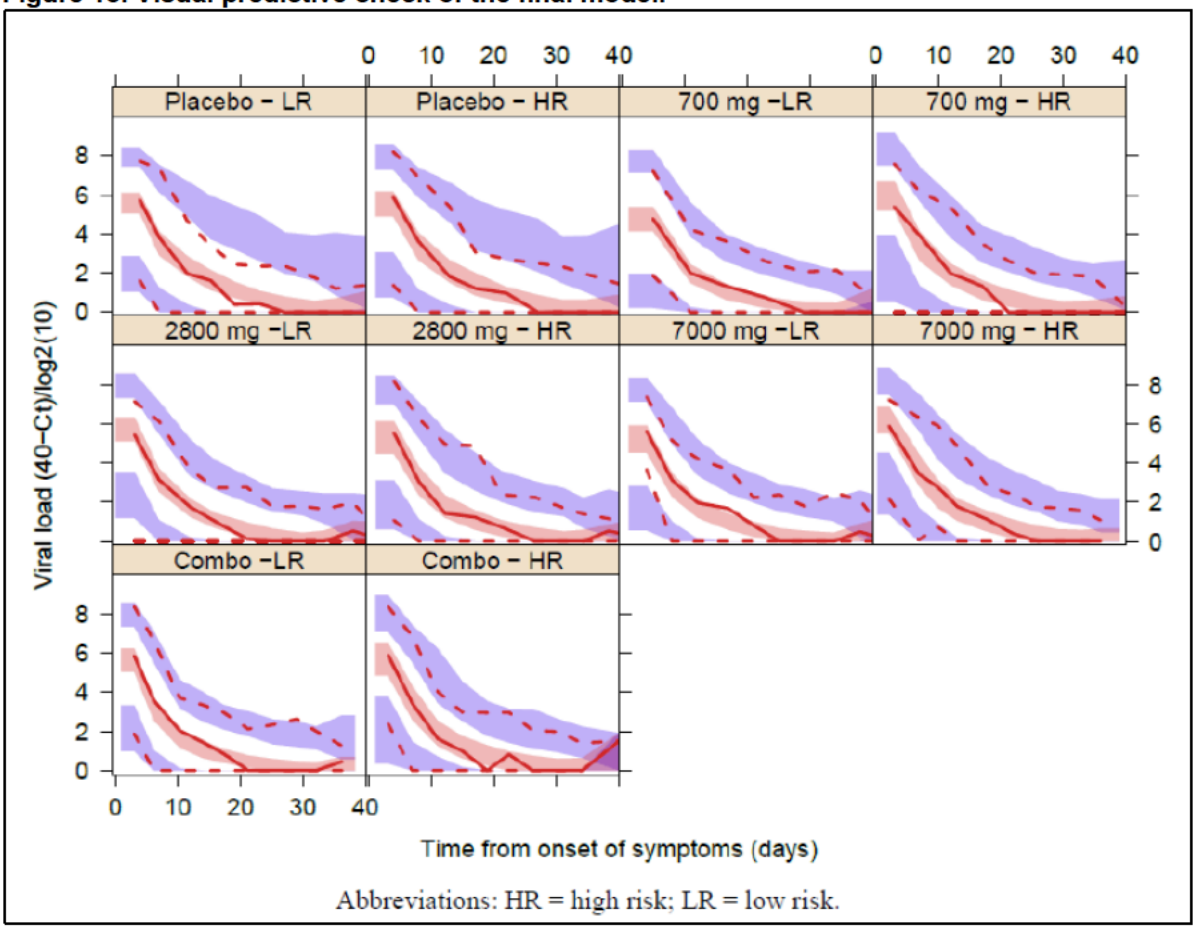


**Figure 13. Visual predictive check of the final model.**




Abbreviations: HR = high risk; LR = low risk.

## 2.3 Limitation of PK/PD analysis

In the PK/PD analysis, a single 2800 mg dose of etesevimab has been clinically investigated, which covers a relative narrow range of concentrations to estimate the $EC_{50}$ parameter. Therefore, the applicant used the relative potency from the *in vitro* antiviral ratio. To evaluate this assumption, we reevaluated the model while estimating the $EC_{50}$ value of etesevimab without this assumption. The $EC_{50}$ value of etesevimab was estimated within a reasonable range (0.24 - 10 µg/mL), and a 11-fold efficacy margin was retained using the most conservative $EC_{90}$ estimate. In conclusion, the *in vitro* anti-viral ratio was reasonable to be applied for the *in vivo* relative potency in PK/PD modeling.

Reviewer comments:
The viral dynamic model described the observed data well However, the residual remained large, which led to uncertainties in parameter estimation, especially $EC_{50}$. The applicant assumed a fixed hill coefficient and the $EC_{50}$ ratio of 3 which were evaluated in **Reviewer's Independent Analysis**. With sensitivity analysis, we concluded that the large margin of serum concentration

over $EC_{90}$ value by day 29 was retained given that $EC_{90}$ estimates stabilized within a reasonable range.

# Reviewer's Independent Analysis

## *1. Viral dynamic model verification*

The verification of the model was carried out using NONMEM version 7.4.3 in comparison to version 7.4.2 used by the applicant. Convergence failed with 3000 burn-in steps, which was extended to 10000 to allow convergence before reduced stochastic/accumulation with SAEM estimation. The exact values of the parameter estimate in the applicant's model could not be reproduced, but the values in the confirmatory run were close enough except $EC_{50}$ value estimate marked in red in **Table 36**.

**Table 36. Comparison of the key viral dynamic model parameter estimates between the applicant's model and FDA's model.**

| PK parameter estimates | Applicant's model Estimate (%RSE) | FDA's confirmatory run | |
|---|---|---|---|
| | | Value | Bias |
| Target cell pool | $4 \times 10^8$ (Fixed) | $4 \times 10^8$ (Fixed) | - |
| Log10 viral load at onset of symptoms | 7.94 (29.4) | 7.95 (15.4) | 0.13% |
| Infection rate constant, β ($day^{-1}$) | $3.63 \times 10^{-7}$ (22.9) | $3.28 \times 10^{-7}$ (35.7) | -9.6% |
| Production rate of virus, PV ($day^{-1}$) | 0.103 (4.57) | 0.135 (10.1) | 31% |
| Elimination rate of virus, CV ($day^{-1}$) | 1.50 (5.56) | 1.52 (4.6) | 1.3% |
| Death rate of infected cells, DI ($day^{-1}$) | 0.254 (4.49) | 0.265 (5.4) | 4.3% |
| Additive error (log viral load) | 0.874 (1.28) | 0.874 (1.3) | 0% |
| Emax (fractional increase in CV) | 0.683 (10.5) | 0.686 (23.2) | 0.44% |
| EC50 (μg/mL) | 0.459 (35.3) | 0.744 (73.7) | 62% |
| Fractional decrease in Emax for high-risk patients | -0.548 (31.8) | -0.516 (23.6) | -5.8% |

## *2. Check the model assumptions*

The applicant assumed a fixed hill coefficient of 4 and $EC_{50}$ ratio of 3 between etesevimab and bamlanivimab. Therefore, we performed independent analysis to test the appropriateness of such assumptions.

### 2.1 Is the fixed hill coefficient appropriate?

The fixed hill coefficient was reasonable compared to an estimated exponent of 3.56 in FDA's independent analysis of viral dynamics using data with bamlanivimab monotherapy. The parameters were estimated with good precision (%RSE < 30%) except the infection rate (%RSE = 31%) which was only marginally higher than 30%. Provided viral data with one etesevimab dose has been investigated (2800 mg) and the uncertainties remain large, the same fixed hill

coefficient was applied for etesevimab. A large hill coefficient is likely to overestimate $EC_{50}$ value. This is a conservative approach for checking the efficacy margin, ensuring PK concentrations are greater than a high estimate of $EC_{50}$ would potentially increase the margin of concentrations produced by the dose and those needed for efficacy.

## 2.2 Is the $EC_{50}$ value of etesevimab estimable?

Bamlanivimab and etesevimab are neutralizing IgG1 mAbs to the spike protein of SARS-CoV-2. They have different but overlapping epitopes on SARS-CoV-2 RBD sites. In vitro neutralization activity of bamlanivimab and etesevimab against SARS-CoV-2 demonstrated a dose-response with $EC_{50}$ values = 0.14 nM and 0.97 nM against USA/WA/1/2020 clinical isolate, and $EC_{50}$ values = 0.34 nM and 0.83 nM against the Italy-INMI1 clinical isolate. Therefore, the ratio of in vitro anti-viral potency of bamlanivimab to etesevimab is 2 to 7 depending on the strain. In the viral dynamics model, the $EC_{50}$ ratio between etesevimab and bamlanivimab was assumed to be 3. The relative potency varies among viral strains; therefore, the current assumption may not be optimal.

Further, we observed a large RSE for the $EC_{50}$ value estimate (**Table 36**), suggesting a poor precision of this parameter estimate. This could be attributed to either insufficient data for estimating bamlanivimab $EC_{50}$ value or a suboptimal assumption for the $EC_{50}$ ratio. The former cause is unlikely because we were able to estimate bamlanivimab $EC_{50}$ value with good precision using data of bamlanivimab alone (see **Reviewer's Independent Analysis 2.1**).

As such, sensitivity analysis was conducted to estimate etesevimab $EC_{50}$ value without the assumption of $EC_{50}$ ratio of 3. The reviewer initialized this parameter at 0.1×, 0.5×, 1×, 2×, 3×, 5×, 10×, 20× $EC_{50}$ value of bamlanivimab. This approach was preferred over fixing the relative potency because the objective function values (OFV) generated by IMP could be insensitive with a large remaining variability and thus may not be a good comparator among models.

To ensure successfully convergence, burn-in steps were increased to 10000. A more stringent test (CTYPE=3, p=0.05) for convergence was used for the largest initial values 20× to reduce the occurrence of local optima. Of note, the OFV minimally changed among models. The final estimates of etesevimab $EC_{50}$ value and their corresponding $EC_{90}$ value (see formula in 3.2 for EC90 calculation) were summarized in **Table 37**.

Given the effect of etesevimab was likely plateaued at 2800 mg dose, the precision of EC50 estimate based on a small change of response was expected to be impacted by large between-subject variability. Nonetheless, the estimates of bamlanivimab $EC_{50}$ value and $EC_{50}$ ratio stabilized within a reasonable range ($EC_{50}$ value: 0.24 - 10 μg/mL, $EC_{50}$ ratio: 0.12× - 11×). The final estimates relative to the initial values gravitated towards a center. In other words, when the initial values

were low, the estimates ended up being larger than the initial values, whereas when the initial values were high, the estimates ended up being smaller than the initial values. Notably, the $EC_{50}$ value estimates initialized with 10× and 20× the $EC_{50}$ value of bamlanivimab were very close.

Following the 700 mg IV infusion of bamlanivimab, the median serum concentration on day 29 was 22 µg/mL (90% CI: 10.7 to 41.6 µg/mL), resulting in approximately an 18-fold efficacy margin over the estimated *in vivo* $EC_{90}$ value. This efficacy margin suggested a near-maximal antiviral response for 700 mg bamlanivimab dose.

The proposed 1400mg etesevimab dose, which is half of the dose in PYAB study, has not been clinically tested. Given a proportional and linear PK for the 700-7000 mg IV dose range, the concentrations achieved with the 1400 mg dose are expected to be half of those from the 2800 mg dose. The median serum concentration on day 29 is estimated to be 111 µg/mL (90% CI: 57.4 to 199 µg/mL) following 1400 mg IV infusion of etesevimab. The highest $EC_{90}$ estimate was used to predict the most conservative efficacy margin, which was 11-fold (90% CI: 6- to 20-fold). This efficacy margin suggested a near-maximal antiviral response for 1400 mg etesevimab dose.

Taken together, the combination of 700 mg bamlanivimab and 1400 mg etesevimab administered together is expected to produce comparable antiviral response to the combination dose (2800 mg each) evaluated in the clinical study PYAB.

**Table 37. EC50 and EC90 estimates of etesevimab in sensitivity analysis.**

| Initial Value | | Estimated EC50 (%RSE) | | Estimated EC50 ratio | Derived EC90 | | Efficacy Margin | |
|---|---|---|---|---|---|---|---|---|
| Ete EC50 (µg/mL) | EC50 ratio (Ete/Bam) | Bam | Ete | | Bam | Ete | Bam | Ete |
| 0.06 | 0.1× | 0.658 (20%) | 0.139 (27%) | 0.12× | 1.14 | 0.24 | 19 | 463 |
| 0.3 | 0.5× | 0.728 (30%) | 0.467 (39%) | 0.64× | 1.26 | 0.81 | 17 | 137 |
| 0.6 | 1× | 0.629 (30%) | 0.84 (77%) | 1.34× | 1.09 | 1.45 | 20 | 77 |
| 1.2 | 2× | 0.639 (57%) | 1.17 (36%) | 1.83× | 1.11 | 2.03 | 18 | 55 |
| 1.8 | 3× | 0.682 (23%) | 1.7 (35%) | 2.49× | 1.18 | 2.94 | 17 | 38 |
| 3 | 5× | 0.701 (26%) | 2.79 (149%) | 3.98× | 1.21 | 4.83 | 17 | 23 |
| 6 | 10× | 0.731 (58%) | 4.43 (47%) | 6.06× | 1.27 | 7.67 | 16 | 14 |
| 12 | 20× | 0.521 (31%) | 5.8 (14%) | 11.1× | 0.9 | 10.0 | 22 | 11 |

Initial value of bamlanivimab $EC_{50}$ value was 0.6 µg/mL in the sensitivity analysis. Efficacy margins were calculated with 22 mg/L of bamlanivimab and 111 mg/L of etesevimab on day 29.

# Appendix 2. Fact Sheet for Health Care Providers

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

## AUTHORIZED USE

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 progressing to severe COVID-19 and/or hospitalization.

### LIMITATIONS OF AUTHORIZED USE

- 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.

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.

**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 progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.**

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
    - cardiovascular disease, OR
    - hypertension, OR
    - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 – 17 years of age AND have
    - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
    - sickle cell disease, OR
    - congenital or acquired heart disease, OR
    - neurodevelopmental disorders, for example, cerebral palsy, OR
    - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
    - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

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

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.

- 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.

- Based on analyses of the available nonclinical, clinical, and virologic data, as well as pharmacokinetic/pharmacodynamic modeling, the authorized dosage of 700 mg bamlanivimab and 1,400 mg etesevimab is expected to have similar clinical effect to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab *[see Dosage (2.2)]*.

- 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.
- 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.

**Contraindications**
None.

**Dosing**

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

Patient Selection and Treatment Initiation
This section provides essential information on 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 progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.

High risk is defined as patients who meet at least one of the following criteria:
- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease

- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
    - cardiovascular disease, OR
    - hypertension, OR
    - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 – 17 years of age AND have
    - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
    - sickle cell disease, OR
    - congenital or acquired heart disease, OR
    - neurodevelopmental disorders, for example, cerebral palsy, OR
    - a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
    - asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Dosage

The dosage of bamlanivimab and etesevimab 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) is:

- bamlanivimab 700 mg
- etesevimab 1,400 mg.

Administer bamlanivimab and etesevimab together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

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

*Rationale for Authorized Dosage*

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

- Available data demonstrate that a dosage of 700 mg bamlanivimab and 1,400 mg etesevimab administered together has similar antiviral activity to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab administered together, which is also supported by in vitro data and pharmacokinetics/pharmacodynamics (PK/PD) modeling *[see Clinical Trial Results and Supporting Data for EUA (18.2) and Pharmacodynamics (14.2)]*.
- A dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab administered together reduced COVID-19 related hospitalizations and deaths in addition to

significantly reducing viral load relative to placebo *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*.
- Bamlanivimab and etesevimab administered together resulted in fewer treatment-emergent variants relative to bamlanivimab alone *[see Microbiology/Resistance Information (15)]*.

Based on analyses of the available nonclinical, clinical, and virologic data, as well as supportive data from pharmacokinetic/pharmacodynamic modeling, the authorized dosage of 700 mg bamlanivimab and 1,400 mg etesevimab is expected to have similar clinical effect to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab.

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[a] in Patients Weighing 50 kg or More**

| **Drug[a]: 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 |

[a] 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[a]: 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[b] | 266 mL/hr | 70 minutes |

[a] 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.
[b] 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 with and without 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 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, dizziness and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Clinical Worsening After Bamlanivimab Administration

Clinical worsening of COVID-19 after administration of bamlanivimab has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.

Limitations of Benefit and Potential 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]*:

- 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, Clinical Trials Experience (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 progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.
- 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.

**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 progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.
2. 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.
3. Patients with known hypersensitivity to any ingredient of bamlanivimab or etesevimab must not receive bamlanivimab and etesevimab.
4. The prescribing health care provider and/or the provider's designee are/is 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 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, or

- By using a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by 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.

5. The prescribing health care provider and/or the provider's designee are/is to provide mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of bamlanivimab and etesevimab.
6. 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
      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 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. Additional information on COVID-19 treatments 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 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.[3] As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

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 in certain high-risk patients 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.

## CONTACT INFORMATION

For additional information visit
www.BAMandETE.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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[3] The health care provider should visit 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.

# FULL EUA PRESCRIBING INFORMATION

**FULL EUA PRESCRIBING INFORMATION: CONTENTS***



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

## 1 AUTHORIZED USE

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 progressing to severe COVID-19 and/or hospitalization.

**LIMITATIONS OF AUTHORIZED USE**

- 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)]*.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Patient Selection

The optimal dosing regimen for treatment of COVID-19 has not yet been established.
The recommended dosing regimen may be updated as data from clinical trials become available.

Bamlanivimab and etesevimab should be administered together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to severe COVID-19 and/or hospitalization.

High risk is defined as patients who meet at least one of the following criteria:

- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥65 years of age
- Are ≥55 years of age AND have
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease.
- Are 12 – 17 years of age AND have
  - BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
  - sickle cell disease, OR

- congenital or acquired heart disease, OR
- neurodevelopmental disorders, for example, cerebral palsy, OR
- a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
- asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

### 2.2 Dosage

The dosage of bamlanivimab and etesevimab 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) is:

- bamlanivimab 700 mg
- etesevimab 1,400 mg.

Administer bamlanivimab and etesevimab together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

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

*Rationale for Authorized Dosage*

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

- Available data demonstrate that a dosage of 700 mg bamlanivimab and 1,400 mg etesevimab administered together has similar antiviral activity to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab administered together, which is also supported by in vitro data and pharmacokinetics/pharmacodynamics (PK/PD) modeling *[see Pharmacodynamics (14.2)]*.
- A dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab administered together reduced COVID-19 related hospitalizations and deaths in addition to significantly reducing viral load relative to placebo *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*.
- Bamlanivimab and etesevimab administered together resulted in fewer treatment-emergent variants relative to bamlanivimab administered alone *[see Microbiology/Resistance Information (15)]*.

Based on analyses of the available nonclinical, clinical, and virologic data, as well as supportive data from pharmacokinetic/pharmacodynamic modeling, the authorized dosage of 700 mg bamlanivimab and 1,400 mg etesevimab is expected to have similar clinical effect to a dosage of 2,800 mg bamlanivimab and 2,800 mg etesevimab.

### 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[a] in Patients Weighing 50 kg or More**

| **Drug[a]: 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 |

[a] 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[a] in Patients Weighing Less Than 50 kg**

| **Drug[a]: 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[b] | 266 mL/hr | 70 minutes |

[a] 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.

[b] 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 with and without 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 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, dizziness and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

### 5.2 Clinical Worsening After Bamlanivimab Administration

Clinical worsening of COVID-19 after administration of bamlanivimab has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.

### 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 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]*:

- 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

Approximately 1,500 subjects have been exposed to bamlanivimab and etesevimab administered together in clinical trials in ambulatory (non-hospitalized) subjects at doses of bamlanivimab 700 mg and etesevimab 1,400 mg or higher. More than 3,900 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 770 subjects *[see Clinical Pharmacology (14.2)]*.

### 6.1 Clinical Trials Experience

The safety of bamlanivimab and etesevimab administered together is based on data from the Phase 2/3 BLAZE-1 trial of ambulatory subjects with COVID-19. The authorized dose is bamlanivimab 700 mg and etesevimab 1,400 mg administered together *[see Dosage (2.2)]*.

BLAZE-1 is a randomized, double-blind, placebo-controlled clinical trial in ambulatory adults with mild to moderate COVID-19 symptoms who had sample collection for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion.

Phase 2 Data from BLAZE-1
Five hundred seventy-seven (577) subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=112), bamlanivimab alone at doses of 700 mg (N=101), 2,800 mg (N=107), or 7,000 mg (N=101) or placebo (N=156).

Based on Phase 2 data from BLAZE-1 subjects followed for at least 28 days after treatment, adverse events occurred in 18% of subjects treated with both bamlanivimab and etesevimab and 28% of placebo-treated subjects.

Nausea was the most commonly reported adverse event, reported by 4% of subjects treated with bamlanivimab and etesevimab together and 4% treated with placebo. Pruritus and pyrexia were more frequently reported from subjects treated with both bamlanivimab and etesevimab (2% and 1%) compared to placebo (1% and 0%, respectively).

Phase 3 Data from BLAZE-1
Five hundred eighteen (518) subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg together and 517 subjects were treated with a single infusion of placebo in Arms 7 and 8, respectively, of the BLAZE-1 Phase 3 trial. Adverse events occurred in 13% of subjects who received 2,800 mg of bamlanivimab and 2,800 mg etesevimab together, and in 12% of placebo-treated subjects. The most common adverse events were nausea, dizziness, and rash. These events each occurred in 1% of subjects treated with bamlanivimab and etesevimab and in 1% of placebo subjects.

Hypersensitivity Including Anaphylaxis and Infusion-related Reactions:
Across ongoing, blinded clinical trials, a case of anaphylaxis and other cases of serious infusion-related reactions were reported with infusion of bamlanivimab with and without etesevimab. The infusions were stopped. All reactions required treatment, one required epinephrine. All events resolved.

Other Immediate Hypersensitivity Events
In the phase 2 portion of BLAZE-1, 2% of subjects treated with bamlanivimab and etesevimab, and 1% of placebo-treated subjects experienced immediate hypersensitivity events. Reported events of pruritus, flushing and hypersensitivity were mild and one case of face swelling was moderate.

In the phase 3 portion of BLAZE-1, 1% of subjects treated with bamlanivimab and etesevimab experienced immediate hypersensitivity events, including 2 infusion-related reactions (moderate severity), 2 cases of rash (1 mild, 1 moderate), 1 infusion site rash (mild), and 1 mild case of pruritus. All events resolved *[see Warnings and Precautions (5.1)]*.

## 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 Clinical Trials Experience (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 is mandatory. The prescribing healthcare provider and/or the provider's designee are/is responsible for the mandatory reporting of all medication errors and the following serious adverse events occurring during the use of bamlanivimab and etesevimab and considered to be potentially related to bamlanivimab and etesevimab. These adverse events must be reported within 7 calendar days from the onset of the event:

- 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, or
- Use a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by 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:

- In section A, box 1, provide the patient's initials in the Patient Identifier
- In section A, box 2, provide the patient's date of birth

- In section B, box 5, description of the event:
    - Write “bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)” as the first line
    - 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.
- In section G, box 1, name and address:
    - Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    - 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
  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

The safety and effectiveness of bamlanivimab and etesevimab administered together are being assessed in adolescent patients in ongoing clinical trials. The recommended dosing regimen is expected to result in comparable serum exposures of bamlanivimab and etesevimab in patients 12 years of age and older and weighing at least 40 kg as observed in adults, based on a pharmacokinetic (PK) modeling approach which accounted for effect of body weight changes associated with age on clearance and volume of distribution.

### 11.4 Geriatric Use

Of the 112 patients receiving bamlanivimab and etesevimab in BLAZE-1, 12% were 65 years of age and older and 2% 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.

### 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 IgG1κ 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 IgG1κ 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). This flat exposure-response relationship was assessed using available clinical data and pharmacokinetic/pharmacodynamic modeling *[see Clinical Trial Results and Supporting Data for EUA (18.2)]*.

### 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 (Cmax) 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 (Cmax) 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/hr (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/hr (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 in pediatric patients have not been evaluated.

Using modeling and simulation, the recommended dosing regimen is expected to result in comparable plasma exposures of bamlanivimab and etesevimab in pediatric patients ages 12 years of age or older who weigh at least 40 kg as observed in adult patients *[see Use in Specific Populations (11.3)]*.

*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 $EC_{50}$ 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 $EC_{50}$ value(s).

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to both bamlanivimab and etesevimab.

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. Neutralization assays using SARS-CoV-2, vesicular stomatitis virus-based pseudovirus, or binding assessment if pseudovirus construction was unsuccessful (E484D), confirmed reductions in susceptibility to the selecting antibody. Retention of susceptibility to the other antibody alone was observed, with the exception of the Q493R substitution. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of those with E484K, E484Q, and Q493R substitutions, which had reduced susceptibility of 15-fold, 22-fold, and >100-fold, respectively in a pseudovirus assay.

Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing. Pseudoviral 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. Pseudovirus harboring spike substitutions K417N + E484K + N501Y together had reduced susceptibility to bamlanivimab or etesevimab alone of >60-fold and >23-fold, respectively, indicating that bamlanivimab and etesevimab together are likely to have reduced activity against viral variants harboring these concurrent substitutions, such as those from B.1.351 (South African origin). Studies are in process to test the activity of bamlanivimab and etesevimab together against additional pseudoviruses and viral variants from this lineage and the related P.1 (Brazilian origin) lineage. Bamlanivimab alone and bamlanivimab and etesevimab together retained activity against pseudovirus expressing del69-70 + N501Y found in the B.1.1.7 variant (UK origin).

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab- and etesevimab-resistance associated spike variations in clinical trials. Detection of phenotypically confirmed bamlanivimab- or etesevimab-resistant variants in baseline samples were observed at

a frequency of 0% (0/14) in the Phase 1 clinical study PYAA and 0.4% (2/523) in clinical study BLAZE-1.

In BLAZE-1, treatment-emergent variants were detected at spike protein amino acid positions K417, D420, N460, E484, F490 and S494, and included K417N, D420N, N460T, E484A/D/G/K/Q/V, F490L/S/V and S494L/P substitutions. Only K417N, D420N, N460T, E484D/K/Q, F490S and S494P have been assessed phenotypically to date. At positions K417, D420, N460, E484, F490 and S494, 9.2% (9/98) and 6.1% (6/98) of participants in the 700 mg bamlanivimab arm harbored such a variant post-baseline at ≥15% and ≥50% allele fractions, respectively. For subjects treated with bamlanivimab and etesevimab, the variant frequencies were 3.9% (4/102) and 0% (0/102) at ≥15% and ≥50% allele fractions, respectively. The majority of the variants were first observed on Day 7 following treatment initiation. Some of the variants were detected in individuals at more than one time point in the 700 mg bamlanivimab arm: 4/9 and 4/6 at ≥15% and ≥50% allele fractions, respectively; however, in the bamlanivimab and etesevimab arm there were no such observations (0/4 at ≥15% allele fraction). When the genotypic analysis was restricted to high-risk participants, the 700 mg bamlanivimab arm showed a 14.0% (6/43) and 9.3% (4/43) variant frequency for the ≥15% and ≥50% allele fractions, respectively, and no variants were detected in the bamlanivimab and etesevimab arm. The clinical relevance of these findings is not 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 $\log_{10}$ 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 $\log_{10}$ 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

The data supporting this EUA are based on analyses of data from the Phase 2/3 BLAZE-1 trial (NCT04427501) and the Phase 2 BLAZE-4 trial (NCT04634409). Both trials are evaluating the safety and efficacy of bamlanivimab and etesevimab together for treatment of subjects with mild to moderate COVID-19. BLAZE-1 provides clinical efficacy data from subjects receiving 2,800 mg bamlanivimab and 2,800 mg of etesevimab together. BLAZE-4 provides comparative virologic outcome data from subjects receiving 700 mg bamlanivimab and 1,400 mg etesevimab (the authorized doses), subjects receiving 2,800 mg bamlanivimab and 2,800 mg of etesevimab, and placebo.

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

BLAZE-1 is an ongoing 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.

Phase 2 Data from BLAZE-1

In the Phase 2 portion of the trial, subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=112), bamlanivimab alone (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) or placebo (N=156). The data are from an interim analysis after all enrolled subjects completed at least Day 29 of the trial.

At baseline, median age was 45 years (with 12% of subjects aged 65 or older); 55% of subjects were female, 89% were White, 43% were Hispanic or Latino, and 6% were Black or African American; 42% of subjects were considered high risk (as defined in Section 2). Subjects had mild (78%) to moderate COVID-19 (22%); the mean duration of symptoms was 5 days; mean viral load by cycle threshold (CT) was 24 at baseline. The baseline demographics and disease characteristics were well balanced across treatment groups.

The pre-specified primary endpoint in this Phase 2 trial was change in viral load from baseline to Day 11 for 2,800 mg bamlanivimab and 2,800 mg etesevimab-treated subjects versus placebo. Most subjects, including those receiving placebo, effectively cleared virus by Day 11 (Figure 1).

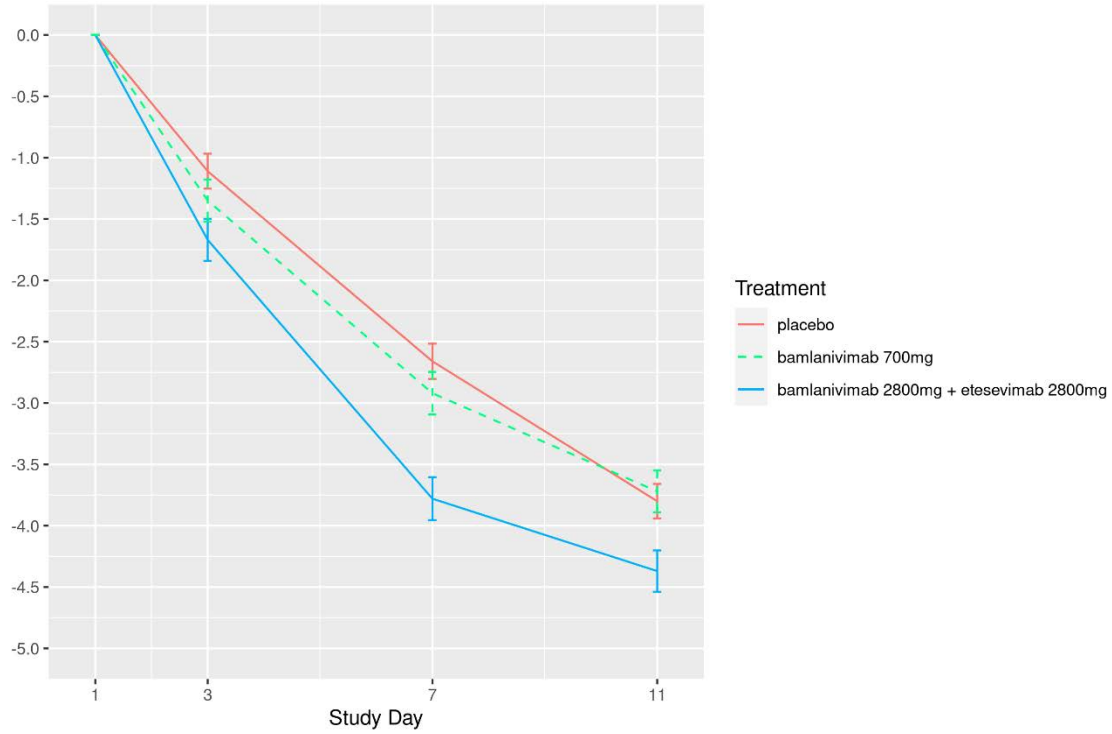


**Figure 1: SARS-CoV-2 Viral Load Change from Baseline by Visit from the Phase 2 Portion of BLAZE-1.**

While viral load was used to define the primary endpoint in this Phase 2 trial, the most important evidence that bamlanivimab and etesevimab may be effective came from the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. A lower proportion of bamlanivimab and etesevimab-treated subjects progressed to COVID-19-related hospitalization or emergency room visits compared to placebo-treated subjects (Table 3). No deaths occurred in any treatment arm.

**Table 3: Proportion of Subjects with Events of Hospitalization or Emergency Room Visits within 28 Days After Treatment**

| Treatment | N[a] | Events | Proportion of Subjects % |
|---|---|---|---|
| Placebo | 156 | 9 | 6% |
| Bamlanivimab and etesevimab[b] | 112 | 1 | 1% |
| Bamlanivimab[c] 700 mg | 101 | 1 | 1% |

[a] N = number of treated patients in analysis.
[b] The doses for bamlanivimab and etesevimab were bamlanivimab 2,800 mg and etesevimab 2,800 mg.
[c] Results for other doses of bamlanivimab were suggestive of a flat dose-response relationship for this endpoint.

The absolute risk reduction for bamlanivimab and etesevimab-treated subjects compared to placebo is greater in subjects at higher risk of hospitalization according to the high risk criteria (Table 4).

**Table 4: Proportion of Subjects with Events of Hospitalization or Emergency Room Visits for Subjects at Higher Risk of Hospitalization**

| Treatment | N[a] | Events | Proportion of Subjects % |
|---|---|---|---|
| Placebo | 68 | 7 | 10% |
| Bamlanivimab and etesevimab[b] | 38 | 1 | 3% |
| Bamlanivimab[c] 700 mg | 46 | 1 | 2% |

[a] N = number of treated patients in analysis.
[b] The doses for bamlanivimab and etesevimab were bamlanivimab 2,800 mg and etesevimab 2,800 mg.
[c] Results for other doses of bamlanivimab were suggestive of a flat dose-response relationship for this endpoint.

The median time to symptom improvement as recorded in a trial specific daily symptom diary was 6 days for bamlanivimab and etesevimab-treated subjects, as compared with 8 days for placebo-treated subjects. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent.

Phase 3 Data from BLAZE-1

In the Phase 3 portion of the trial, 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 (as defined in Section 2).

At baseline, median age was 56 years (with 31% of subjects aged 65 or older); 52% of subjects were female, 87% were White, 29% were Hispanic or Latino, and 8% were Black or African American. Subjects had mild (77%) to moderate (23%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 24 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 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 ($p<0.001$).

At Day 7, 29% of subjects treated with placebo and 10% of subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together had persistently high viral loads ($p<0.000001$), which was defined as SARS-CoV-2 viral load >5.27.

Secondary endpoints include mean change in viral load from baseline to Day 3, 5, and 7 (Figure 2).

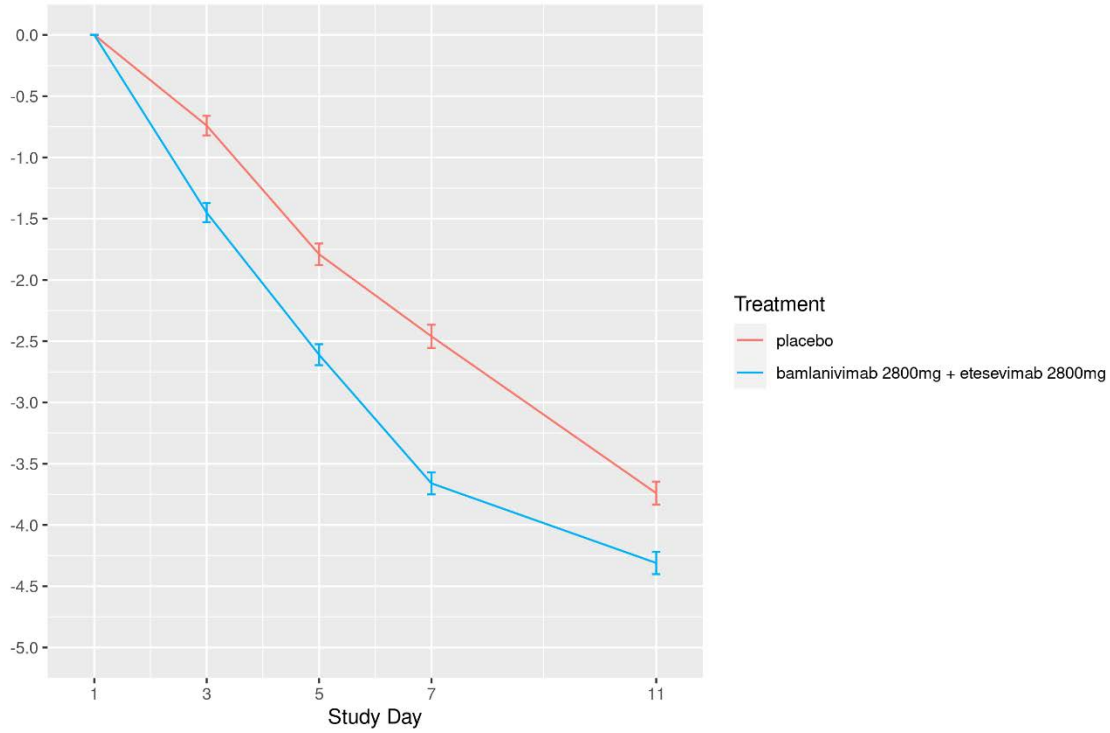


**Figure 2: SARS-CoV-2 Viral Load Change from Baseline by Visit from the Phase 3 Portion of BLAZE-1.**

### 18.2 Mild to Moderate COVID-19 (BLAZE-4)

BLAZE-4 is an ongoing 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 with COVID-19 symptoms who are not hospitalized). BLAZE-4 enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity, and excluded subjects ≥65 years old or with BMI ≥35. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects were treated with a single infusion of bamlanivimab 700 mg and etesevimab 1,400 mg (N=158), bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=101), bamlanivimab alone at a dose of 700 mg (N=103), or placebo (N=153). Results are not yet complete for additional arms in this trial.

At baseline, median age was 39 years (with 1% of subjects aged 65 or older); 50% of subjects were female, 87% were White, 29% were Hispanic or Latino, and 6% were Black or African American; 8% of subjects were considered high risk (as defined in Section 2). Subjects had mild (84%) to moderate (16%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 25 at baseline. The baseline demographics and disease characteristics were well balanced across treatment groups.

The pre-specified primary endpoint in this Phase 2 trial was the proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days). The rates were 31% (42/135) for placebo, 14% (21/147, p<0.001 versus placebo) for bamlanivimab 700 mg and etesevimab 1,400 mg together, and 10% (10/99, p<0.001 versus placebo) for bamlanivimab 2,800 mg and etesevimab 2,800 mg together.

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

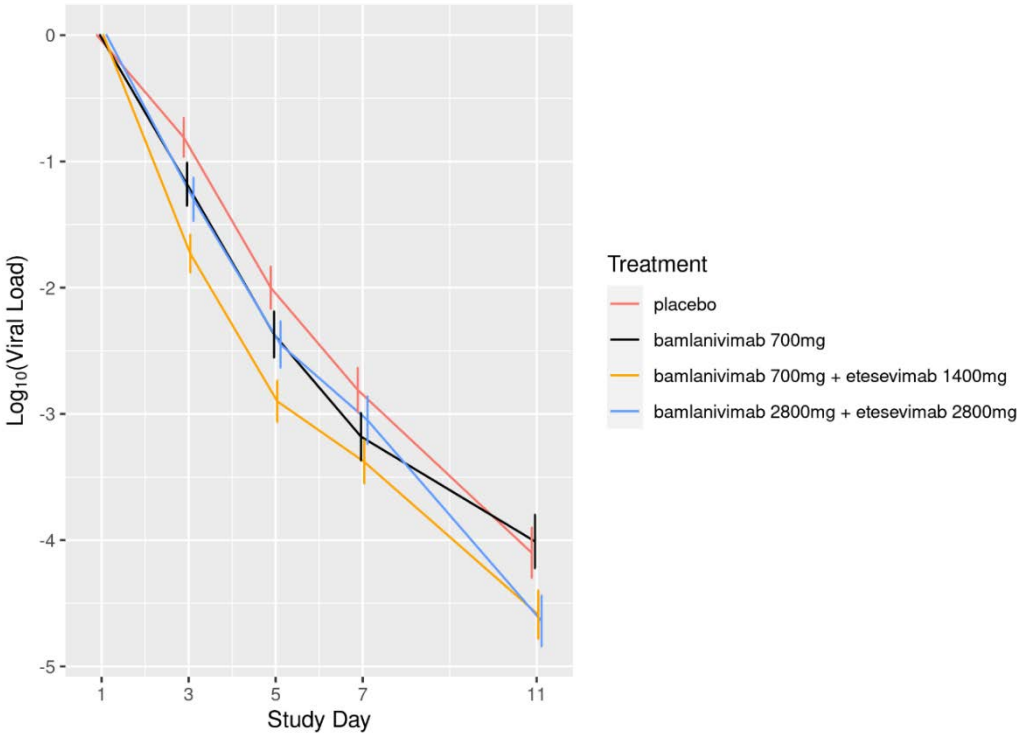


**Figure 3: SARS-CoV-2 Viral Load Change from Baseline by Visit from Phase 2 Trial BLAZE-4.**

## 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.

Bamlanivimab and etesevimab are supplied as:

| Antibody | Concentration | Package Size | NDC |
|---|---|---|---|
| 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.BAMandETE.com

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

Literature issued February 09, 2021

**Eli Lilly and Company, Indianapolis, IN 46285, USA**



12.0-ETE-0000-EUA HCP-20210209

# Appendix 3. Fact Sheet for Patients and Parent 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 of coronavirus disease 2019 (COVID-19). This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking bamlanivimab and etesevimab, which you may receive.

Receiving bamlanivimab and etesevimab together may benefit certain people with COVID-19.

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. 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, seem to be 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 to treat mild to moderate symptoms of COVID-19 in adults and adolescents (12 years of age and older who weigh at least 88 pounds (40 kg)), and who are at high risk for developing severe COVID-19 symptoms or the need for hospitalization. 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 treat people with COVID-19.

The FDA has authorized the emergency use of bamlanivimab and etesevimab together for the treatment 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
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- 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, dizziness, and sweating. These reactions may be severe or life threatening.
- Worsening symptoms after treatment: You may experience new or worsening symptoms after infusion, 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.covid19treatmentguidelines.nih.gov/ 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 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, 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.BAMandETE.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 or cleared product. The FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, and available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that the product meets certain criteria for safety, performance, and labeling and may be effective in treatment of patients during the COVID-19 pandemic. All of these criteria must be met to allow for the product to be used in the treatment of patients 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 product may no longer be used).

Literature issued February 09, 2021

**Eli Lilly and Company, Indianapolis, IN 46285, USA**



6.0-ETE-0000-EUA PAT-0210209

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