SEE ATTACHED ADDENDUM

Emergency Use Authorization (EUA) for Bebtelovimab (LY-CoV1404)

Center for Drug Evaluation and Research (CDER) Review

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	111
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Eli Lilly and Company Christine Phillips, PhD, RAC Advisor, Global Regulatory Affairs - NA Mobile: (b) (6) Email: phillips_christine_ann@lilly.com
Manufacturer, if different from Sponsor	Eli Lilly and Company
Submission Date(s)	January 7, 2022
Receipt Date(s)	January 7, 2022
OND Division / Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)/Discipline(s)	Natalie Pica, MD, PhD – Clinical Reviewer Wendy Carter, DO – Cross Discipline Team Lead Michael Thomson, PhD – Clinical Virology Reviewer Jules O'Rear, PhD – Clinical Virology Team Lead Wen Zeng, PhD – Statistics Reviewer Thamban Valappil, PhD – Statistics Team Lead Karen Higgins, ScD – Supervisory Mathematical Statistician, Division of Biometrics IV Xing Jing, PhD – Clinical Pharmacology Reviewer Su-Young Choi, PharmD, PhD – Clinical Pharmacology Team Lead Kellie Reynolds, PharmD – Division Director, DIDP Justin Earp, PhD – Pharmacometrics Team Lead

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Integrated Review Completion Date	February 11, 2022
Proprietary Name	n/a
Established Name/Other names used during development	bebtelovimab (LY-CoV1404)
Dosage Forms/Strengths	bebtelovimab - 175mg 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 progression to severe COVID-19, including hospitalization or death
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 bebtelovimab 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[1] for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

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 bebtelovimab 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 progression to severe COVID-19, including hospitalization and death and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate, and when used under such conditions, the known and potential benefits of

[1] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

bebtelovimab outweigh the known and potential risks of the drug.

There is no adequate, approved, and available alternative to the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. Bebtelovimab is a neutralizing IgG1 monoclonal antibody that binds to an epitope 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 bebtelovimab. Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. On January 21, 2022, the Agency approved a supplemental new drug application (sNDA) to New Drug Application (NDA) 214787 approving Veklury for the treatment of 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, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[2]

Veklury is administered via daily intravenous infusion for a total treatment duration of 3 days. Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to bebtelovimab for this authorized use because it may not be feasible or practical in certain patients (e.g., it requires a 3-day treatment duration).

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

Proposed Use Under EUA:

We recommend authorization of bebtelovimab 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[3] for progression to severe COVID-19, including hospitalization or death, **and**

[2] On October 22, 2020, FDA initially approved Veklury for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) requiring hospitalization.

[3] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[4]

- Bebtelovimab is not authorized for use in patients:
    - who are hospitalized due to COVID-19, OR
    - who require oxygen therapy due to COVID-19, OR
    - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, 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 bebtelovimab for adults and pediatric patients (12 years of age and older weighing ≥40 kg) is a single intravenous (IV) infusion of 175 mg.

Administer bebtelovimab as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset.

Bebtelovimab must be administered as a single intravenous injection over at least 30 seconds.

Pregnant or Lactating Patients:

[4] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

No dosage adjustment is recommended for pregnant or lactating patients. Bebtelovimab 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 dosage adjustment is recommended based on age (12 to 86 years of age), sex, race, body weight (41 to 173 kg), renal or mild hepatic impairment, or for disease severity. Bebtelovimab has not been studied in patients with moderate or severe hepatic impairment. Refer to Section XI for more details.

IV. Product Information (Dose Preparation and Administration)

General Information

- Bebtelovimab should be prepared by a qualified healthcare professional using aseptic technique.
- Inspect bebtelovimab vial visually for particulate matter and discoloration. Bebtelovimab is clear to opalescent and colorless to slightly yellow to slightly brown solution. Discard the vial if the solution is cloudy, discolored or visible particles are observed.
- Bebtelovimab may only be administered in settings in which healthcare 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.
- **Clinically monitor patients for possible infusion-related reactions during administration and observe patients for at least 1 hour after injection is complete.**

Materials Needed for Administration

- 1 bebtelovimab vial (175 mg/2 mL)
- 1 disposable polypropylene dosing syringe capable of holding 2 mL
- 1 polycarbonate and polyvinylchloride without di-ethylhexylphthalate (DEHP) syringe extension set
- 0.9% Sodium Chloride Injection for flushing

Preparation

- Remove bebtelovimab vial 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 vial. Inspect the vial.**
- Withdraw 2 mL from the vial into the disposable syringe.
- Discard any product remaining in the vial.
- This product is preservative-free and therefore, should be administered immediately.

- If immediate administration is not possible, store the syringe 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]). If refrigerated, allow the prepared syringe to equilibrate to room temperature for approximately 20 minutes prior to administration.

- Attach the syringe extension set**.**
- Prime the extension set.
- Administer the entire contents of the syringe via IV injection over at least 30 seconds.
- After the entire contents of the syringe have been administered, **flush the extension set** with 0.9% Sodium Chloride to ensure delivery of the required dose.

How Supplied/Storage and Handling
Bebtelovimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

Antibody	Concentration	Package Size	NDC
Bebtelovimab	175 mg/2 mL (87.5 mg/mL)	One vial per carton	0002-7589-01

Storage and Handling
Bebtelovimab 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.

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

Background Information on the Condition

The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death. At present, the Omicron variant is circulating at high frequency in the United States.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, more than 394 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported globally as of February 7, 2022, including an estimated 5.7 million

deaths.[5] As of February 9, 2022, approximately 76 million cases of COVID-19, with more than 903,000 deaths, have been reported in the United States according to CDC.[6]

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. Older age, underlying medical conditions, as well as other factors (for example, race and ethnicity), may also place individual patients at increased risk for progression to severe COVID-19.[7]

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

Treatment Alternatives

There is no adequate, approved, and available alternative to the emergency use of bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg), with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization and death, and for whom alternative COVID-19 treatment options are not accessible or clinically appropriate.

There are 6 other products that are approved or authorized for the treatment of mild-to-moderate COVID-19.

- Bamlanivimab and etesevimab administered together, REGEN-COV (casirivimab and imdevimab), and sotrovimab are other monoclonal antibody therapies that are authorized to treat adult and pediatric patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. On January 24, 2022, a limitation of authorized use was added to bamlanivimab and etesevimab administered together and to REGEN-COV. These products are not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency. Bamlanivimab and etesevimab, as well as REGEN-COV, are not thought to retain activity against the Omicron variant based on nonclinical data that assessed

[5] https://covid19.who.int/. Accessed February 7, 2022.
[6] https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-proportions.html#cases_casesper100klast7days. Accessed February 9, 2022
[7] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed January 28, 2022.

neutralization activity. Given the high frequency of the Omicron variant at this time, these products are not currently authorized in any U.S. region. Sotrovimab is thought to retain activity against the Omicron variant and therefore is currently authorized for use in all U.S. geographic regions.

- Paxlovid™ includes nirmatrelvir, a SARS-CoV-2 main protease (Mpro, also referred to as 3CLpro or nsp5 protease) inhibitor and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor. This oral medication is authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.
- Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis and is only authorized for use in adults. Molnupiravir is authorized for treatment of mild-to-moderate COVID-19 in adults:
    - with positive results of direct SARS-CoV-2 viral testing, and
    - who are at high risk for progression to severe COVID-19, including hospitalization or death and for
    - whom alternative COVID-19 treatment options authorized or approved by FDA are not accessible or clinically appropriate.
- Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir (Veklury) is approved for the treatment 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, who are not hospitalized and are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

Other products are approved or authorized for the prevention of COVID-19 or the treatment of hospitalized patients with COVID-19; however, this is beyond the scope of this review which is focused on the non-hospitalized, mild-to-moderate COVID-19 population.

VI. Related Regulatory Submission(s)

Bebtelovimab has been studied under INDs 154936 and 150440.

- Related Master Files (Product Quality reviewer to provide this information)
    - DMF (b) (4)
        - DMF Title: (b) (4)
        - Master File holder: (b) (4)

VII. Summary of Clinical Data

The primary data to support the authorization of bebtelovimab for the treatment of mild-to-moderate COVID-19 was generated from Trial J2X-MC-PYAH (PYAH; BLAZE-4).

Trial PYAH was a phase 1/2, placebo-controlled, double-blind, randomized, single-dose trial in participants with mild-to-moderate COVID-19 conducted under IND 150440. This trial studied bebtelovimab alone, as well as bebtelovimab administered together with bamlanivimab and etesevimab in Addendum 4 (phase 1) and in Arms 9-14 (phase 2) (highlighted). Addendum 4, the phase 1 portion of the trial evaluating dose and safety, is included only for safety analyses and not in the efficacy analyses. See Table 1 for additional details.

Table 1: All Clinical Trials

Study Number	IND, NDA, or Literature Reference	Type of Study (PK, Efficacy, Safety)	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
J2X-MC-PYAH (BLAZE-4)	150440	Efficacy, Safety	N = 1416 Mild-to-moderate COVID-19 Addendum 2 N = 66	Phase 1/2, placebo-controlled, double-blind, randomized, single-dose trial in participants with mild-to-moderate COVID-19 illness Treatment Arms 1-5 were in parallel Arms 1-3 continued and were in parallel with Arm 6 Treatment Arms 7 and 8: in parallel with each other Treatment Arms 9-11: double blind, low risk participants Treatment Arms 12 and 13: high risk participants randomized 2:1,	Single IV infusion; Arm B (b) (4) • Arm 1: Placebo • Arm 2: 175 mg BAM + 350 mg ETE • Arm 3: 700 mg BAM + 1400 mg ETE • Arm 4: 2800 mg BAM + 2800 mg ETE • Arm 5: 700 mg BAM • Arm 6: 350 mg BAM + 700 mg ETE • Arm 7: 700 mg BAM + 500 mg VIR-7831 • Arm 8: Placebo • Arm 9: 175 mg LY3853113 • Arm 10: 175 mg LY3853113 + 700 mg BAM + 1400 mg ETE • Arm 11: Placebo • Arm 12: 175 mg LY3853113 • Arm 13: 175 mg LY3853113 + 700 mg BAM + 1400 mg ETE • Arm 14: 175 mg LY3853113	Arms 1-8, Addendum 2: Active, enrollment complete Enrollment N = 719 Arms 1-6: Arm 1: N = 153 Arm 2: N = 103 Arm 3: N = 158 Arm 4: N = 101 Arm 5: N = 103 Arm 6: N = 101 Arms 7 and 8: N = 202 Arm 7: 101 Arm 8: 101 Arms 9-14 N = 706 Arms 9-11: N = 380 Arm 9: Blinded Arm 10: Blinded Arm 11: Blinded Arms 12-13:

				parallel and open label Treatment Arm 14: high risk participants, open-label, to enroll following completion of enrollment in Arms 12 and 13 Addendum 2: Open-label substudy to explore accelerated IV administration of BAM alone and with ETE Addendum 4: Open-label phase 1, double blind, randomized, placebo-controlled, ascending dose substudy in low risk participants to characterize the safety and tolerability of LY3853113 (BEB) alone by IV infusion [redacted] and together with BAM and ETE	+ 700 mg BAM + 1400 mg **Addendum 2:** • Arm A: 700 mg BAM • Arm B: 700 mg BAM + 1400 mg ETE **Addendum 4:** • Arm A (IV): ◦ Dose 1: 70 mg LY3853113 at 140mg/min ◦ Dose 2a: 175 mg LY3853113 at 140mg/min ◦ Dose 2b: 175 mg LY3853113 at 350mg/min ◦ Dose 2c: 175 mg LY3853113 + 700 mg BAM + 1400 mg ETE triple combo at 350mg/min ◦ Dose 3: 1750 mg LY3853113 at 250 mg/min • Arm B [redacted] ◦ Dose 1: [redacted] LY3853113 ◦ Dose 2: [redacted] LY3853113	N = 150 Arms 12-14: Open-label Arm 14: N = 176 Addendum 2 N = 66 Addendum 4: N = 56** Arm A (IV) Dose 1: N = 6 Dose 2a: N = 6 Dose 2b: N = 6 Dose 2c: N = 6 Dose 3: N = 6 Pooled placebo: N = 10 Arm B [redacted] Dose 1: N = 6 Dose 2: N = 6

Source: Adapted from Applicant Submission to EUA 94 dated February 2, 2022 entitled "Updated Table of Clinical Studies (as of February 2022)."

**In Arm A Dose 2A, 1 participant did not meet study criteria but was inadvertently randomized. Patient was discontinued prior to administration of study drug. Overall, 56 participants were randomized and received study drug in Addenda 4.

Abbreviations: BAM = bamlanivimab/LY3819253/LY-CoV555COVID-19 = coronavirus disease 2019; Enrolled = entered and randomized; ETE = etesevimab/LY3832479/LY-CoV016, IND = investigational new drug; IV = intravenous; BEB = bebtelovimab/LY3853113/LY-CoV1404; N = number of participants; PK = pharmacokinetics; [redacted]

VIII. Human Clinical Efficacy

The main source of clinical efficacy data submitted to support the EUA request for bebtelovimab comes from the phase 2 portion of Trial PYAH (also called BLAZE-4), Arms 9 to 14. Bebtelovimab alone and bebtelovimab with bamlanivimab and etesevimab were evaluated in low and high risk subjects with mild-to-moderate COVID-19 in Arms 9-14. The efficacy data submitted are from a database lock on August 27, 2021, when all participants reached Day 29.

The phase 2 efficacy results from PYAH are presented in this section. The outcomes in the low risk population (Arms 9-11) are presented first, followed by outcomes in the high risk population (Arms 12-13 and Arm 14). The antiviral resistance data submitted to support bebtelovimab are discussed at the end of this section. The database lock dates for the analyses of baseline virology data were October 03, 2021 and October 12, 2021 due to the lag time associated with sequencing of the samples.

Overview of Trial PYAH (BLAZE-4)

Trial PYAH (BLAZE-4, clinicaltrials.gov identifier NCT04634409) is a randomized, single-dose trial in participants with mild-to-moderate COVID-19. Table 2 summarizes the arms of PYAH that are relevant to this efficacy review.

- Arms 9 to 11 were conducted in a low risk population. Arms 9 to 11 were double-blinded and placebo-controlled, and had a 1:1:1 randomization ratio.
- Arms 12 to 14 were conducted in a high risk population without a placebo comparator. At the time of study conduct, there were other authorized treatments available for patients at high risk of COVID-19 progression and a placebo arm was not included. Subjects in Arms 12 and 13 were randomized with a 2:1 ratio during May, 2021. The enrollment of Arm 14 was opened in June of 2021 after Arms 12 and 13 were fully enrolled. There was no randomization for Arm 14.

Arms 9 to 14 evaluated bebtelovimab alone, and in combination with bamlanivimab and etesevimab (Table *2*).

Table 2: Treatment Arms in Trial PYAH Assessing Bebtelovimab

Treatment Arm	Dose, Volumes, and Route of Administration	Participant Population / Randomization	Number of Subjects
Arm 9: BEB	175 mg, 62.5 mL, and IV	Low-risk population double-blinded, placebo controlled, with 1:1:1 randomization ratio	125
Arm 10: BAM +ETE +BEB	700mg+1400mg+175mg, 62.5 mL, and IV		127
Arm 11: PBO	62.5 mL saline, and IV		128
Arm 12: BEB	175mg, 2.5 mL, and IV	High-risk population with open-label with 2:1 randomization ratio	100 (1 adolescent)
Arm 13: BAM +ETE+BEB	700mg+1400mg+175mg, 62.5 mL, and IV		50 (1 adolescent)
Arm 14: BAM +ETE +BEB	700mg+1400mg+175mg, 62.5 mL, and IV	High-risk population with open-label, no randomization	176 (2 adolescent)

Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab
Source: EUA Request and IND 154936 SDN 0061.

Inclusion criteria for enrollment in Trial PYAH Arms 9-14 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.

Additionally, participants enrolled into Arms 9-11 were characterized as low risk. These participants were at least 18 years of age and less than 65 years of age, did not have the risk factors defined for high-risk participants in Arms 12 and 13, had a BMI under 35 kg/m^2, and had not received SARS-CoV-2 vaccine.

Participants enrolled into Arms 12-14 were characterized as high risk. Adult participants at least 18 years of age enrolled in Arms 12 and 13 were characterized as high risk if they satisfied at least 1 of the following risk factors at the time of screening:

- were at least 65 years of age
- had a BMI of at least 35 kg/m^2
- had chronic kidney disease
- had type 1 or type 2 diabetes
- had immunosuppressive disease
- were currently receiving immunosuppressive treatment, or
- were at least 55 years of age AND had
    - cardiovascular disease, OR
    - hypertension, OR
    - chronic obstructive pulmonary disease or other chronic respiratory disease.

Adolescent participants, 12 to 17 years of age (inclusive), enrolled in Arms 12 and 13 were characterized as high risk if they satisfied at least 1 of the following risk factors at the time of screening:

- had a BMI greater than the 85th percentile for their age and gender based on CDC growth charts (CDC 2017)
- had sickle cell disease
- had congenital or acquired heart disease
- had neurodevelopmental disorders, for example, cerebral palsy
- had a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)
- had asthma or reactive airway or other chronic respiratory disease that requires daily medication for control
- had type 1 or type 2 diabetes
- had chronic kidney disease
- had immunosuppressive disease, or
- were currently receiving immunosuppressive treatment.

Participants enrolled in Arm 14 were at least 12 years of age and characterized as high risk if they satisfied at least 1 of the following risk factors at the time of screening:

- were at least 65 years of age

- were adults (at least 18 years of age) with BMI greater than 25 kg/m^2, or if age 12 to 17, had BMI at least or greater than the 85th percentile for their age and gender based on CDC growth charts (CDC 2017)
- had chronic kidney disease
- had type 1 or type 2 diabetes
- had immunosuppressive disease
- were currently receiving immunosuppressive treatment
- had cardiovascular disease (including congenital heart disease) or hypertension
- had chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- had sickle cell disease
- had a neurodevelopmental disorder (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies), or
- had a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19]).

Efficacy Results for PYAH Treatment Arms 9-11 in the Low Risk Population

Table 3 below displays the demographic and baseline characteristics of Arms 9-11. All 380 subjects were enrolled from the U.S. Slightly over half of participants were female (56%). Approximately 79% were White and 19% were Black or African American; 36% were Hispanic or Latino. The median age was 35 years. Seventy-four percent of subjects had only mild symptoms and 26% of subjects had at least one moderate COVID-19 symptom. The mean duration of symptom onset to randomization was 3.6 days; the mean normalized viral load was 6.13 at baseline (which corresponds to CT value of 24.63). The baseline demographics and disease characteristics were well balanced across treatment arms with the exception of baseline serology status. A higher percentage of subjects in the placebo arm were seropositive at baseline (15% vs. 9% of subjects in the bebtelovimab with bamlanivimab and etesevimab arm and 7% of subjects in the bebtelovimab alone arm). No subjects enrolled in Arms 9-11 had received SARS-CoV-2 vaccines at baseline.

Table 3: Baseline Demographics and Disease Characteristics in Trial PYAH (Arms 9-11)

Baseline Factor	**Arm 11: Placebo (N=128)**	**Arm 9: BEB (N=125)**	**Arm 10: BAM +ETE +BEB (N=127)**	**Pooled Active (N=252)**	**Overall (N=380)**
Female	72 (56%)	63 (50%)	76 (60%)	139 (55%)	211 (56%)
Race: White	90 (74%)	97 (83%)	99 (81%)	196 (82%)	286 (79%)
Race: Black or African American	29 (24%)	19 (16%)	19 (16%)	38 (16%)	67 (19%)
Hispanic or Latino	45 (35%)	46 (37%)	45 (35%)	91 (36%)	136 (36%)
Age (median years)	34	34	37	36	35
Severity of COVID-19: Mild	101 (79%)	84 (67%)	97 (76%)	181 (72%)	282 (74%)

Severity of COVID-19: Moderate	27 (21%)	41 (33%)	30 (24%)	71 (28%)	98 (26%)
Duration of symptoms onset to randomization (days, mean)	3.80	3.55	3.50	3.53	3.62
Baseline log_{10} viral load (mean)[1]	5.99	6.43	5.98	6.20	6.13
Serology at Baseline: Positive	18 (15.0%)	8 (6.9%)	11 (9.3%)	19 (8.1%)	37 (10.5%)
Serology at Baseline: Negative	102 (85.0%)	108 (93.1%)	107 (90.7%)	215 (91.9%)	317 (89.5%)
Serology at Baseline: Missing	8	9	9	18	26

Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab

[1] Ct values were converted on the log10 scale and normalized to RNAseP using this formula: $(45\text{-}Ct_{Ni})/(\log_2 10)$ based on N1 (primary) and N2 (secondary) Ct values.

Source: EUA Request and IND 154936 SDN 0061.

Endpoints for Arms 9-11

The prespecified primary efficacy endpoint for these treatment arms was the proportion of participants with persistently high viral load (PHVL), defined as SARS-CoV-2 viral load greater than 5.27 on Day 7. Secondary efficacy endpoints included mean change in viral load from baseline to Days 3, 5, 7, and 11; time to sustained symptom resolution; and the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29.

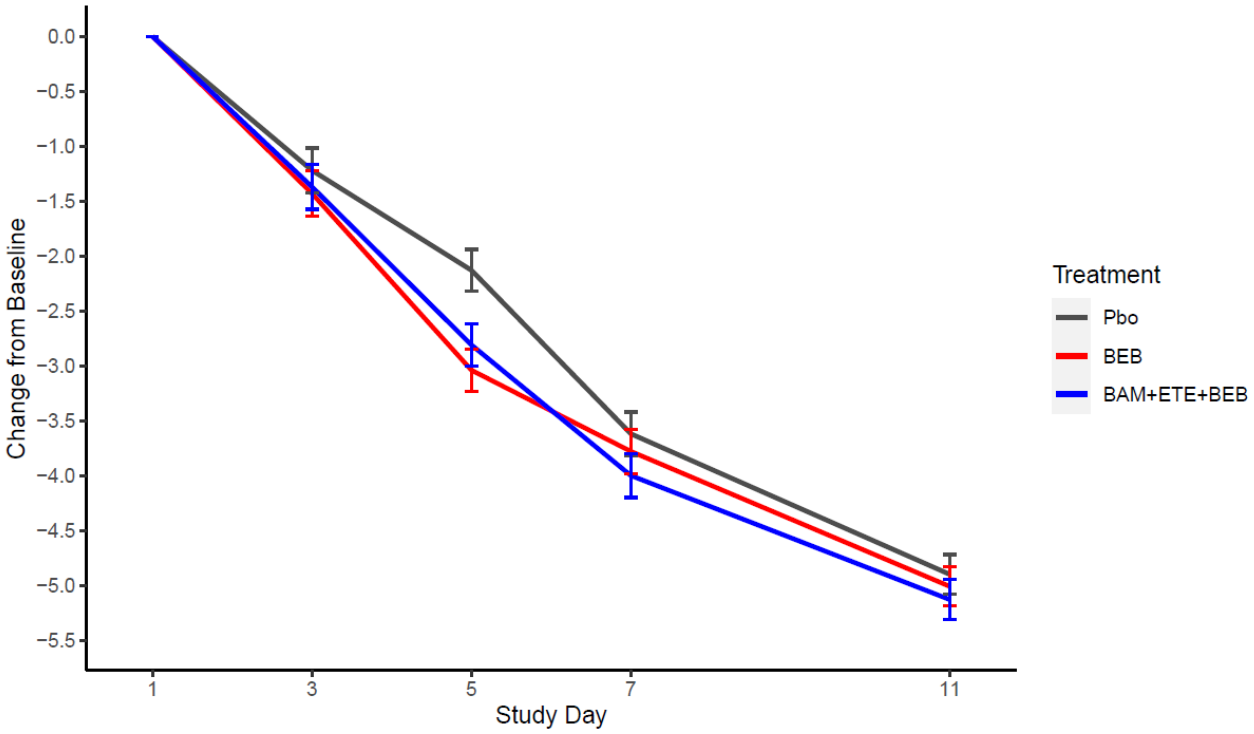
According to the SAP for Arms 9-11, time to sustained symptom resolution is defined as 2 consecutive assessments in the symptom questionnaire with a score of 0 for shortness of breath, feeling feverish, body aches and pains, sore throat, chills, and headache; and a score of 0 or 1 for cough and fatigue. Time to sustained symptom resolution was defined (in days) as: the first study day when sustained symptom resolution status is changed to “Yes” – Infusion Date + 1.

Virologic Outcomes for Arms 9-11

PHVL occurred in 26 subjects (21%) in the placebo arm as compared to 17 subjects (14%) in the bebtelovimab alone arm (p=0.147), and 16 subjects (13%) in the bebtelovimab with bamlanivimab and etsevimab together arm (p=0.098). Neither comparison of test arm to placebo was statistically significant. The relative reduction of PHVL was 34% (95% CI: -15%, 62%) for bebtelovimab alone and 38% (95% CI: -9%, 65%) for bebtelovimab with bamlanivimab and etesevimab together. Because of the lack of significant results of the primary endpoint, the p-values in the remaining analyses should be interpreted with caution given the lack of type I error control.

Changes from baseline to Day 3, 5, 7, and 11 in mean SARS-CoV-2 viral load were secondary endpoints. Viral load reduction in participants who received bebtelovimab alone and bebtelovimab with bamlanivimab and etesevimab was demonstrated on Day 5 (Figure 1 and Table 4 below). However, the clinical meaningfulness is unclear because an effect was not found at the other time points as subjects in the placebo arm also showed similar viral load reductions as the test arms at later time points. The change from baseline in mean viral load was similar for bebtelovimab and bebtelovimab with bamlanivimab and etesevimab (Figure 1 and Table 4).

Figure 1: SARS-CoV-2 Normalized Viral Load Change from Baseline (Mean ± SE) by Visit of Low-Risk Adults in Trial PYAH (Arms 9-11)



Source: EUA submission on 2/4/2022

Table 4: Normalized Viral Load of SARS-CoV-2 Change from Baseline in Trial PYAH (Arms 9-11)[1]

Timepoint	Arm 11: Placebo (N=126)		Arm 9: BEB (N=125)		Arm 10: BAM+ETE+BEB (N=126)	
	LSM[2]		LSM	p-value	LSM	p-value
Day 3	-1.22		-1.43	0.464	-1.37	0.588
Day 5	-2.13		-3.04	**<0.001**	-2.81	**0.012**
Day 7	-3.62		-3.78	0.565	-4.00	0.175
Day 11	-4.90		-5.01	0.675	-5.13	0.382
Day 29	-6.16		-6.42	0.126	-6.25	0.573

[1]: The number of subjects who had viral load measurements varied among visits. On Day 11, the missing percentages are approximately 15% (19/128) in placebo arm, 10% (13/125) in BEB alone arm, and 17% (21/127) in BAM+ETE+BEB arm. No imputation of missing data was conducted.
[2]: LSM: least square mean change from baseline; p-value comes from a mixed model with repeated measures which includes log base 10 transformed baseline as a covariate, and treatment, day, treatment-by-day interaction as fixed effects.
Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab.
Source: EUA Request and IND 154936 SDN 0061 Table APP 92.

The subgroup analyses of viral load reduction for subjects with mild symptom severity at baseline, for subjects with moderate symptom severity at baseline, and for subjects who were seronegative at baseline are shown in Tables 5, 6, and 7 below. The patterns were similar to those seen when data from all participants in Arms 9-11 were analyzed (Table 4).

Table 5: Subgroup Analysis of Normalized Viral Load of SARS-CoV-2 Change from Baseline in Trial PYAH[1] (Arms 9-11; Baseline Symptom Severity=Mild)

Timepoint	Arm 11: Placebo (N=101)		Arm 9: BEB (N=84)		Arm 10: BAM+ETE+BEB (N=97)	
	LSM[2]		LSM	p-value	LSM	p-value
Day 3	-1.13		-1.47	0.312	-1.35	0.495
Day 5	-2.13		-2.98	**0.008**	-2.88	**0.015**
Day 7	-3.64		-3.88	0.451	-3.80	0.615
Day 11	-5.00		-5.00	0.996	-5.19	0.520
Day 29	-6.06		-6.40	0.081	-6.17	0.557

[1]: The number of subjects who had viral load measurements varied among visits. No imputation of missing data was conducted.
[2]: LSM: least square mean change from baseline; p-value comes from a mixed model with repeated measures which includes log base 10 transformed baseline as a covariate, and treatment, day, treatment-by-day interaction as fixed effects.
Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab; Source: EUA Request, Regulatory Response (Pre EUA submission IR Jan2022) additional analyses, and IND 154936 SDN 0061.

Table 6: Subgroup Analysis of Normalized Viral Load of SARS-CoV-2 Change from Baseline in Trial PYAH[1] (Arms 9-11; Baseline Symptom Severity=Moderate)

Timepoint	Arm 11: placebo (N=27)		Arm 9: BEB (N=41)		Arm 10: BAM+ETE+BEB (N=30)	
	LSM[2]		LSM	p-value	LSM	p-value
Day 3	-1.51		-1.37	0.802	-1.46	0.934
Day 5	-2.09		-3.22	**0.040**	-2.61	0.370
Day 7	-3.55		-3.58	0.959	-4.63	0.081
Day 11	-4.62		-5.04	0.435	-4.98	0.526
Day 29	-6.52		-6.51	0.964	-6.51	0.980

*: The number of subjects who had viral load measure are vary among visits. No imputation of missing data was conducted.
2: LSM: least square mean change from baseline; p-value comes from a mixed model with repeated measures which includes log base 10 transformed baseline as a covariate, and treatment, day, treatment-by-day interaction as fixed effects.
Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab.
Source: EUA Request, Regulatory Response (Pre EUA submission IR Jan2022) additional analyses, and IND 154936 SDN 0061.

Table 7: Subgroup Analysis of Normalized Viral Load of SARS-CoV-2 Change from Baseline in Trial PYAH[1] (Arms 9-11; Baseline Seronegative)

Timepoint	Arm 11: Placebo (N=102)		Arm 9: BEB (N=108)		Arm 10: BAM+ETE+BEB (N=107)	
	LSM[2]		LSM	p-value	LSM	p-value
Day 3	-1.15		-1.58	0.139	-1.53	0.192
Day 5	-2.23		-3.20	**<0.001**	-2.99	**0.009**
Day 7	-3.64		-3.99	0.254	-4.21	0.057
Day 11	-5.14		-5.33	0.510	-5.38	0.409
Day 29	-6.61		-6.91	0.094	-6.59	0.877

*: The number of subjects who had viral load measurements varied among visits. No imputation of missing data was conducted.
2: LSM: least square mean change from baseline; p-value comes from a mixed model with repeated measures which includes log base 10 transformed baseline as a covariate, and treatment, day, treatment-by-day interaction as fixed effects.
Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab.
Source: EUA Request, Regulatory Response (Pre EUA submission IR Jan2022) additional analyses, and IND 154936 SDN 0061.

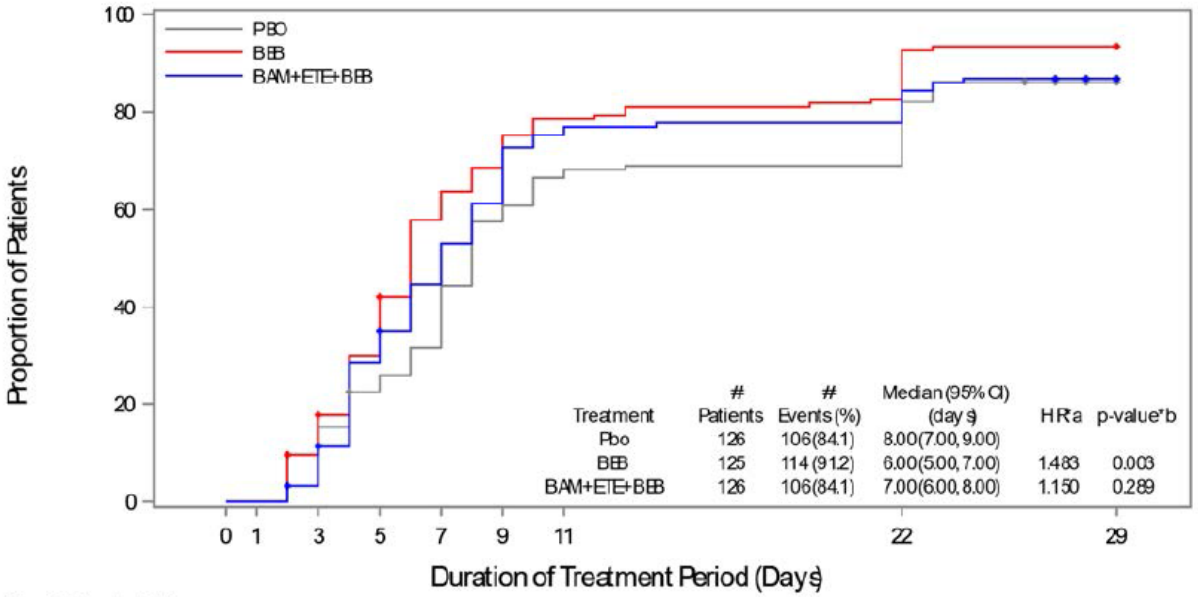
FDA has allowed phase 2 studies to use other virologic endpoints as primary while exploring dose and safety, and collecting clinical outcomes as secondary. The Sponsor selected PHVL as the primary endpoint based on evaluation of data from the study of other monoclonal antibodies that suggested a correlation between PHVL and the risk of progression to severe COVID-19. Other virologic endpoints have also been used in phase 2 trials. For example, in EUA 094, to support authorization of bamlanivimab and etesevimab administered together, the phase 2 trial used a primary efficacy endpoint of change from baseline to Day 11 in SARS-CoV-2 viral load, which is one of the secondary efficacy endpoints in PYAH.

FDA has conducted additional analyses of previous COVID-19 monoclonal antibody treatment trials in high risk outpatients with mild-to-moderate COVID-19. The analyses assessed the correlation between nasopharyngeal viral load and the clinical endpoint of hospitalization or death using different cutoffs and timepoints for the PVHL definition. Viral load was correlated with the clinical endpoint of hospitalization or death; however, the treatment effect on the clinical endpoint was not reliably predicted by the magnitude of the treatment effect on nasopharyngeal viral load. Therefore, viral load was not found to be a surrogate for the clinical endpoint. In particular, the data did not support PHVL as a surrogate for progression to severe COVID-19. These analyses used data generated from clinical trials conducted prior to the emergence of the Omicron variant and because current hospitalization and death rates might differ, it is unclear how these factors could affect our assessment of the surrogate endpoint. Considering these factors, these virologic data showing modest reductions in viral load are considered as part of the totality of evidence to support authorization of bebtelovimab.

Clinical Outcomes for Arms 9-11

Time to sustained symptom resolution is another secondary efficacy endpoint. Using the trial specific daily symptom diary, the median time to sustained symptom resolution was 6 days in the bebtelovimab alone arm (p-value=0.003; 95% CI: 5, 7 days) as compared with 8 days (95% CI: 7, 9 days) in the placebo arm, while the median time to sustained symptom resolution was 7 days in the bebtelovimab with bamlanivimab and etesevimab arm (p-value=0.289; 95% CI: 6, 8 days) (Figure 2 below). The interpretability of symptom resolution may be limited, however, by missing data on symptoms collected through Day 29.

Figure 2: Time to Sustained Symptomatic Resolution Kaplan-Meier Plot in Trial PYAH (Arms 9-11)



Treatment	# Patients	# Events (%)	Median (95% CI) (days)	HR'a	p-value*b
Pbo	126	106(84.1)	8.00(7.00, 9.00)		
BEB	125	114 (91.2)	6.00(5.00, 7.00)	1.483	0.003
BAM+ETE+BEB	126	106(84.1)	7.00(6.00, 8.00)	1.150	0.289

No. of Patients at Risk

Time	0	1	3	5	7	9	11	22	29
Pbo	126(0)	126(19)	105(13)	91(23)	68(20)	48(9)	39(17)	22(5)	6(0)
BEB	125(0)	125(22)	101(30)	70(26)	44(14)	30(4)	26(17)	9(1)	4(0)
BAM+ETE+BEB	126(0)	126(14)	109(29)	79(22)	57(24)	33(5)	28(9)	19(3)	5(0)

Abbreviations: BAM = bamlanivimab; ETE = etesevimab; BEB = bebtelovimab; BEB = BEB 175 mg; BAM+ETE+BEB = BAM 700 mg + ETE 1400 mg + BEB 175 mg; CI = confidence interval; HR = hazard ratio.
Patients at risk displayed under Day x are calculate based on patients whose time to event or censoring > Day x date.
Number of events displayed under Day x are calculated based on events occurred during the time interval from Day x (exduding Week x date) to the day of next reported Day y (including Day y date).
*a HR- unstratified.
*b P-value (2-sided) - log-rank for comparison with Placebo.

Source: IND 154936 SDN 0061, Figure APP 17.

COVID-19 related hospitalization or death is considered the most relevant clinical endpoint. However, as expected, only a small number of low-risk subjects experienced events of hospitalization or death in Arms 9-11 of PYAH. Events occurred in 2 (1.6%) subjects who received placebo as compared with 2 (1.6%) events in those who received bebtelovimab alone, and 3 (2.4%) events in those who received bebtelovimab with bamlanivimab and etesevimab.

Efficacy Results for PYAH Treatment Arms 12-14 in the High Risk Population

Table 8 below displays demographic and baseline characteristics of Arms 12-13. A total of 150 subjects were enrolled; 100 subjects in the bebtelovimab alone arm and 50 subjects in bebtelovimab with bamlanivimab and etesevimab arm. These participants were enrolled at sites in the U.S. Approximately half of participants were female (52%). Seventy-five percent were White and 18% were Black or African American; 18% were Hispanic or Latino. The median age was 50 years. Seventy-five percent of subjects had only mild COVID-19 symptoms and 25% had at least one moderate COVID-19 symptom. The mean duration of

symptom onset to randomization was 4.7 days. The mean viral load was 5.52 at baseline (which is corresponding Ct value of 26.66). Approximately 13% of subjects were seropositive at baseline and 21% of subjects had at least one dose of a COVID-19 vaccine. The baseline demographics and disease characteristics were well balanced between Arm 12 and Arm 13.

Table 8: Baseline Demographics and Disease Characteristics in Trial PYAH (Arms 12-13)

Baseline Factors	Arm 12: BEB (N=100)	Arm 13: BAM+ETE+BEB (N=50)	Pooled: (N=150)
Female	52 (52%)	26 (52%)	78 (52%)
Race: White	78 (78%)	32 (68%)	110 (75%)
Race: Black or African American	14 (14%)	13 (28%)	27 (18%)
Hispanic or Latino	19 (19%)	8 (16%)	27 (18%)
Age (median years)	48.5	52.5	49.5
Severity of COVID-19: Mild	74(74%)	38 (76%)	112 (75%)
Severity of COVID-19: Moderate	26 (26%)	12 (24%)	38 (25%)
Duration of symptoms onset to randomization (days, mean)	4.64	4.70	4.66
Baseline log_{10} viral load (mean)[1]	5.71	5.13	5.52
Seropositive at Baseline	11 (11.3%)	8 (17.0%)	19 (13.2%)
Vaccinated at Baseline	22 (22.0%)	9 (18.0%)	31 (20.7%)
Fully Vaccinated	18	6	24
Partially Vaccinated	4	3	7

[1]Ct values were converted on the log10 scale and normalized to RNAseP using this formula: $(45\text{-}Ct_{Ni})/(\log_2 10)$ based on N1 (primary) and N2 (secondary) Ct values.
Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab
Source: EUA Request and IND 154936 SDN 0061.

Table 9 below displays demographic and baseline characteristics of Arm 14.
Arm 14 evaluated bebtelovimab with bamlanivimab and etesevimab without randomization; there were 176 subjects enrolled. Approximately 56% of subjects were female. The majority of participants were White; 16% were Black or African American and 28% were Hispanic or Latino. The median age was 51 years. Subjects had mild (73%) to moderate (27%) COVID-19 symptoms. The mean duration of symptom onset to randomization was 4.0 days. The mean viral load was 6.49 at baseline (which is corresponding CT value of 23.45). Approximately 6% of subjects were seropositive at baseline and 31% of subjects had at least one dose of a COVID-19 vaccine at baseline.

Table 9: Baseline Demographics and Disease Characteristics in Trial PYAH (Arm 14)

Baseline Factor	Arm14: BAM+ETE+BEB (N=176)
Female	98 (56%)
Race: White	136 (80%)
Race: Black or African American	28 (16%)
Hispanic or Latino	49 (28%)
Age (median years)	51
Severity of COVID-19: Mild	129 (73%)

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Severity of COVID-19: Moderate	47 (27%)
Duration of symptoms onset to randomization (days, mean)	4.00
Baseline log_{10} viral load (mean)	6.49
Seropositive at Baseline	10 (6.0%)
Vaccinated at Baseline	55 (31.3%)
Fully Vaccinated	49
Partially Vaccinated	5

Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab
Source: EUA Request and IND 154936 SDN 0061.

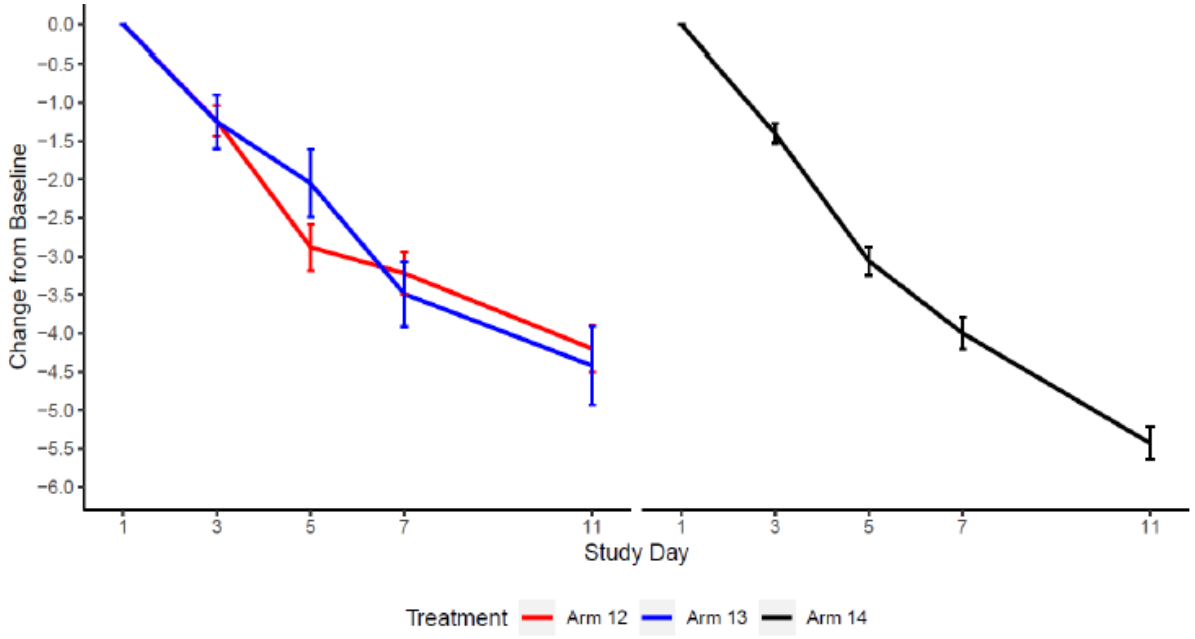
Endpoints for Arm 12-14

The primary objective for these treatment arms was to characterize the safety profile of bebtelovimab 175 mg by evaluating adverse events and serious adverse events. Efficacy endpoints included mean change in viral load from baseline to Days 3, 5, 7, and 11, time to sustained symptom resolution, and the proportion of subjects with COVID-19 related hospitalization or death by any cause by Day 29. There was no concurrent placebo control for these treatment arms, and therefore results are presented here in a descriptive manner.

Virologic Outcomes for Arms 12-14

The patterns of viral load reduction in subjects who received bebtelovimab alone and bebtelovimab with bamlanivimab and etesevimab in this high-risk population were similar to what was observed in Arms 9-11 in the low risk population (Figure 3 and Table 10 below). Comparison of Arms 12 and 13 demonstrate that there was no apparent difference between montherapy with bebtelovimab alone and bebtelovimab with bamlanivimab and etesevimab for change from baseline in mean SARS-CoV-2 viral load. Viral load reduction in Arm 14 was similar to Arms 12 and 13 (Figure 3 and Table 10).

Figure 3: SARS-CoV-2 Normalized Viral Load Change from Baseline (Mean ± SE) by Visit of High-Risk Adults in Trial PYAH (Arms 12-14)



Treatment Arm 12: bebtelovimab alone; Treatment Arm 13: bebtelovimab with bamlanivimab and etesevimab; Treatment Arm 14: bebtelovimab with bamlanivimab and etesevimab
Source: Response to IR submitted February 9, 2022.

Table 10: Viral Load Change from Baseline in Trial PYAH (Arms 12-14)[1]

Timepoint	Arm 12: BEB (N=100)	Arm 13: BAM+ETE+BEB (N=50)	Arm 14: BAM+ETE+BEB (N=176)
Baseline VL	6.42	5.70	7.06
Day 3	-1.24	-1.25	-1.40
Day 5	-2.88	-2.05	-3.06
Day 7	-3.22	-3.49	-4.00
Day 11	-4.20	-4.42	-5.43
Day 29	-5.65	-4.80	-6.72

[1] The number of subjects who had viral load measurements are varied among visits. On Day 11, the missing percentages are approximately 11% (11/100) in BEB arm 12, 14% (7/50) in BAM+ETE+BEB arm 13, and 25% (44/176) in BAM+ETE+BEB arm 14. No imputation of missing data was conducted. Arm 14 enrolled subjects after the enrollment of Arm 12 and 13 were completed.
Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab.
Source: EUA Request and IND 154936 SDN 0061 Table APP 91.

The subgroup analyses of viral load reduction for subjects without vaccination at baseline and who were seronegative at baseline are shown in Tables 11 and 12 below. The patterns were similar to what is shown in Table 10.

Table 11: Subgroup Analysis of Normalized Viral Load of SARS-CoV-2 Change from Baseline in Trial PYAH[1] (Arms 12-14; Subjects Unvaccinated at Baseline)

Timepoint	Arm 12 BEB (N=77)	Arm 13 BAM+ETE+BEB (N=41)	Arm 14 BAM+ETE+BEB (N=121)
Baseline VL	6.81	5.57	7.42
Day 3	-1.45	-1.13	-1.38
Day 5	-3.13	-2.13	-2.85
Day 7	-3.39	-3.40	-4.31
Day 11	-4.65	-4.25	-5.60
Day 29	-6.09	-4.68	-7.01

[1]: The number of subjects who had viral load measurements are varied among visits. No missing data was imputed. Arm 14 enrolled subjects after the enrollment of Arm 12 and 13 were completed.
Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab;
Source: EUA Request, Regulatory Response (Pre EUA submission IR Jan2022) additional analyses, and IND 154936 SDN 0061.

Table 12: Subgroup Analysis of Normalized Viral Load of SARS-CoV-2 Change from Baseline in Trial PYAH[1] (Arms 12-14; Seronegative Subjects at Baseline)

Timepoint	Arm 12 BEB (N=85)	Arm 13 BAM+ETE+BEB (N=39)	Arm 14 BAM+ETE+BEB (N=158)
Baseline VL	6.58	6.02	7.39
Day 3	-1.30	-1.26	-1.46
Day 5	-2.81	-2.20	-3.15
Day 7	-3.25	-3.70	-4.20
Day 11	-4.32	-4.67	-5.70
Day 29	-5.81	-5.07	-6.97

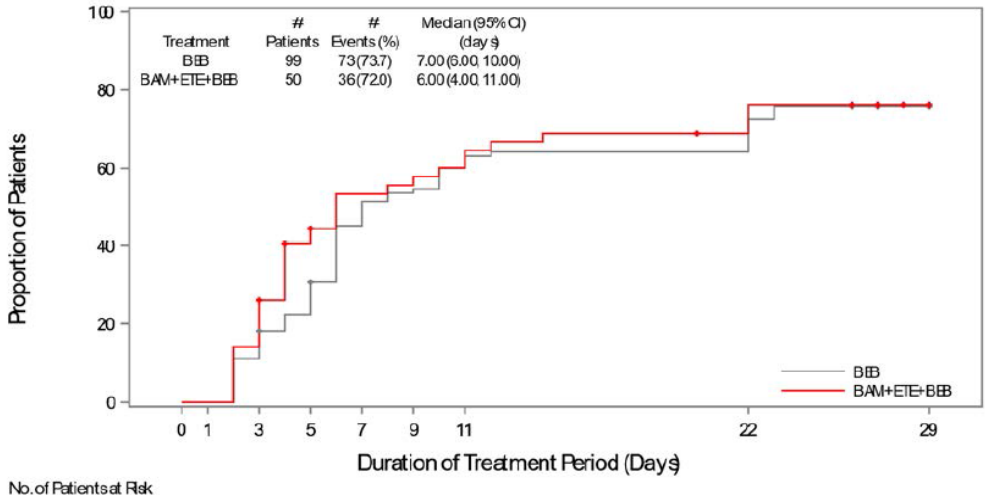
[1]: The number of subjects who had viral load measurements are varied among visits. No missing data was imputed. Arm 14 enrolled subjects after the enrollment of Arm 12 and 13 were finished.
Abbreviations: BEB = bebtelovimab; BAM = bamlanivimab; ETE = etesevimab;
Source: EUA Request, Regulatory Response (Pre EUA submission IR Jan2022) additional analyses, and IND 154936 SDN 0061.

As stated above, virologic endpoints have been correlated with clinical outcomes but a treatment effect on viral load did not reliably predict a treatment effect on the clinical endpoint. The virologic data observed in the high risk Arms 12-14 are considered as part of the totality of evidence to support authorization of bebtelovimab.

Clinical Outcomes for Arms 12-14

Using the trial specific daily symptom diary, the median time to sustained symptom resolution was 7 days in subjects who received bebtelovimab alone as compared to 6 days in subjects who received bebtelovimab with bamlanivimab and etesevimab (arm that was concurrently enrolled; Figure 4). The median time to sustained symptom resolution was 8 days in subject who received bebtelovimab with bamlanivimab and etesevimab in Arm 14 (Figure 5).

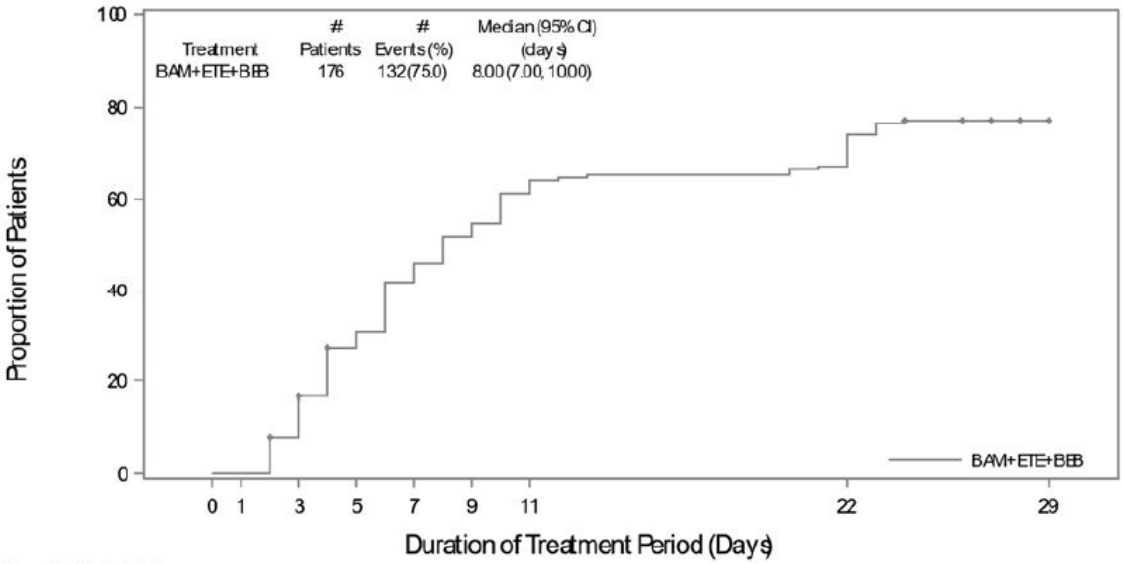
Figure 4: Time to Sustained Symptomatic Resolution Kaplan-Meier Plot in Trial PYAH (Arms 12-13)



Abbreviations: BAM = bamlanivimab; ETE = etesevimab; BEB = bebtelovimab; BEB = BEB 175 mg; BAM+ETE+BEB = BAM 700 mg + ETE 1400 mg + BEB 175 mg.
Patients at risk displayed under Day x are calculate based on patients whose time to event or censoring > Day x date.
Number of events displayed under Day x are calculated based on events occurred during the time interval from Day x (excluding Week x date) to the day of next reported Day y (including Day y date).

Source: IND 154936 SDN 0061, Figure APP 16.

Figure 5: Time to Sustained Symptomatic Resolution Kaplan-Meier Plot in Trial PYAH (Arm 14)



No. of Patients at Risk

Time	0	1	3	5	7	9	11	22	29
BAM+ETE+BEB	176(0)	176(29)	143(24)	118(26)	92(15)	77(16)	61(17)	44(5)	16(0)

Source: IND 154936 SDN 0061, Figure APP 18.

Again, the interpretability of symptom resolution may be limited by missing data on symptoms collected through Day 29.

In the cohorts that enrolled high risk participants, COVID-19 related hospitalization or death occurred at similar rates: 3 (3%) subjects in Arm 12 (bebtelovimab alone), 2 (4%) subjects in Arm 13 (bebtelovimab with bamlanivimab and etesevimab), and in 3 (1.7%) subjects in Arm 14 (bebtelovimab with bamlanivimab and etesevimab).

Summary of Efficacy Results in Arms 9-14

Based on the data from PYAH, bebtelovimab has been shown to improve symptoms in patients with mild-to-moderate COVID-19. While a reduction in the proportion of PHVL was not appreciated, a reduction in SARS-CoV-2 viral load on Day 5 was observed relative to placebo, though the clinical significance of these virologic outcomes are unclear. The placebo-controlled phase 2 data are limited by enrollment of only low risk subjects without risk factors for progression to severe COVID-19, and the trial was not powered or designed to determine a difference in the clinical outcomes of hospitalization or death between the placebo and bebtelovimab treatment arms.

The efficacy analyses for the treatment arms that enrolled high risk participants are limited due to the lack of a concurrent placebo control arm for this population. Additionally, Arms 12 and 13 enrolled concurrently, while Arm 14 enrolled at a later date. A low rate (1.7-4%) of COVID-19 related hospitalization and death through Day 29 was seen in those who received bebtelovimab alone or with bamlanivimab and etesevimab, however, interpretation of these data is limited lack of placebo comparator. In prior monoclonal antibody trials that enrolled high risk patients, the typical rates of hospitalization or death for the placebo group were 3-7%.

However, comparisons to these data are limited as these trials occurred when different viral variants were circulating and baseline factors, such as age, other demographics, and seropositivity rates, varied. Clinical data were similar for bebtelovimab alone as compared to the combination of bebtelovimab with other monoclonal antibodies.

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 was conducted by the Applicant of putative resistance-associated variants in clinical trial PYAH (treatment Arms 9 to 14) focused on amino acid positions in the receptor binding domain (RBD) of the SARS-CoV-2 spike protein which had been identified in non-clinical studies as being important for susceptibility to bebtelovimab: K444, V445, G446 and P499. Viral sequencing and phenotypic analyses are ongoing for clinical trial PYAH (BLAZE-4). An additional analysis was conducted by the FDA of treatment-emergent substitutions occurring at ≥15% and ≥50% allele frequency at all amino acid positions in the spike protein, with a focus on the RBD.

Baseline variants

Baseline sequencing data were available for 611 of the 702 participants from whom nasal samples were collected in trial PYAH (Arms 9 to 14). Most subjects (>90%) were infected with a variant of concern (Table 13). The most common variants were Delta (31.3% of BEB-only arm) and Alpha (41.8% of bebtelovimab-only arm). There was only one instance of a subject in whom a baseline substitution with reduced susceptibility to bebtelovimab was detected, which was G446V (8-fold reduction). No instances of infection with the Omicron variant occurred because the trial was conducted prior to the emergence of this variant in the U.S.

Table 13: SARS-CoV-2 Variant Lineages at Baseline, Arms 9 to 14, Study J2W MC-PYAH

	Placebo	BEB	BAM+ETE+BEB	Total
Alpha	23.1% (25/108)	41.8% (84/201)	21.9% (66/302)	28.6% (175/611)
Beta	0% (0/108)	0.5% (1/201)	0.7% (2/302)	0.5% (3/611)
Gamma	6.5% (7/108)	5.0% (10/201)	5.6% (17/302)	5.6% (34/611)
Delta	60.2% (65/108)	31.3% (63/201)	58.3% (176/302)	49.8% (304/611)
Delta + K417N	0% (0/108)	0.5% (1/201)	1.3% (4/302)	0.8% (5/611)
Iota	0.9% (1/108)	1.5% (3/201)	0% (0/302)	0.7% (4/611)
Lambda	0% (0/108)	0.5% (1/201)	0.7% (2/302)	0.5% (3/611)
Mu	2.8% (3/108)	5.0% (10/201)	3.3% (10/302)	3.8% (23/611)
Non-WHO classified	1.9% (2/108)	4.5% (9/201)	2.3% (7/302)	2.9% (18/611)
Not determined	4.6% (5/108)	9.5% (19/201)	6.0% (18/302)	6.9% (42/611)

Source: Table 7.1, virology genotyping report
BAM = bamlanivimab; BEB = bebtelovimab; ETE = etesevimab

With respect to clinical outcomes, there were 10/611 subjects with baseline sequence data who were hospitalized. These included: 2/175 subjects with Alpha infection in the bebtelovimab with bamlanivimab and etesevimab (high risk) group, 7/304 with Delta, of whom 2 were in bebtelovimab (high risk), 2 in bebtelovimab (low risk), 1 in bebtelovimab with bamlanivimab and etesevimab (high risk), 2 in bebtelovimab with bamlanivimab and

etesevimab (low risk) groups. The one other subject who was hospitalized was in the placebo (low risk) group and infected with a variant of the B.1.1.519 lineage.

Treatment-emergent resistance-associated substitutions

The following substitutions with known phenotypic impact to bebtelovimab (but no impact [<5-fold] to bamlanivimab or etesevimab) were detected as treatment-emergent at ≥1 time point using a ≥15% allele fraction threshold (fold-reduction in susceptibility based on pseudotyped VLP assay):

- K444N (>1,901-fold reduction)
- V445G (>730-fold reduction)
- G446V (8-fold reduction)
- P499H (>1,606-fold reduction)
- P499R (>1,870-fold reduction)

The frequency of detection of these substitutions was as follows:

- 5% (10/199) for bebtelovimab-treated participants (3.6% [4/112] in low-risk subjects, 6.9% [6/87] in high-risk subjects)
- 0.3% (1/312) for participants treated with bebtelovimab with bamlanivimab and etesevimab -
- 0% (0/112) for placebo-treated participants.

Additional treatment-emergent substitutions with no phenotypic data seen in ≥2 subjects at ≥15% or ≥50% allele fraction included: Q321H, C379F and G404C (bebtelovimab with bamlanivimab and etesevimab arms, n=2 each). K444E substitution, occurring at a bebtelovimab epitope contact residue, was also observed at ≥50% allele fraction in 1 subject in the bebtelovimab (low risk) arm.

Table 14 lists the subjects in whom treatment-emergent (TE) resistance-associated substitutions (RAS) were detected, with the baseline variant, Day(s) the substitutions were detected and allele fractions for each substitution/time point. Most substitutions were first detected at Day 5 (n = 3) and Day 7 (n = 6) post-treatment.

Table 14: Subjects in Trial PYAH Arms 9 to 14 in Whom Treatment-Emergent Bebtelovimab Resistance-Associated Substitutions Were Detected (FDA analysis)

Subject ID	Treatment	BEB RAS (Day detected)	Allele fraction [a]	Baseline lineage
(b) (6)	BEB (HR)	P499R (7)	0.963	B.1.634
	BEB (HR)	K444N (7, 11)	0.986, 0.982	Iota (B.1.526-like)
	BEB (HR)	K444N (5), P499R (5, 7, 11)	0.153, 0.253, 0.917, 0.959	Iota (B.1.526-like)
	BEB (HR)	G446V (29), PTN499HTY (29)	0.975, 0.938	Alpha (B.1.1.7-like)
	BEB (HR)	K444N (7, 11), P499R (11)	0.902, 0.803, 0.21	Lambda (C.37-like)
	BEB (HR)	V445G (11), PTN499RTY (11)	0.402, 0.575	B.1.621-like
	BEB (LR)	P499R (5)	0.721	Delta (B.1.617.2-like)

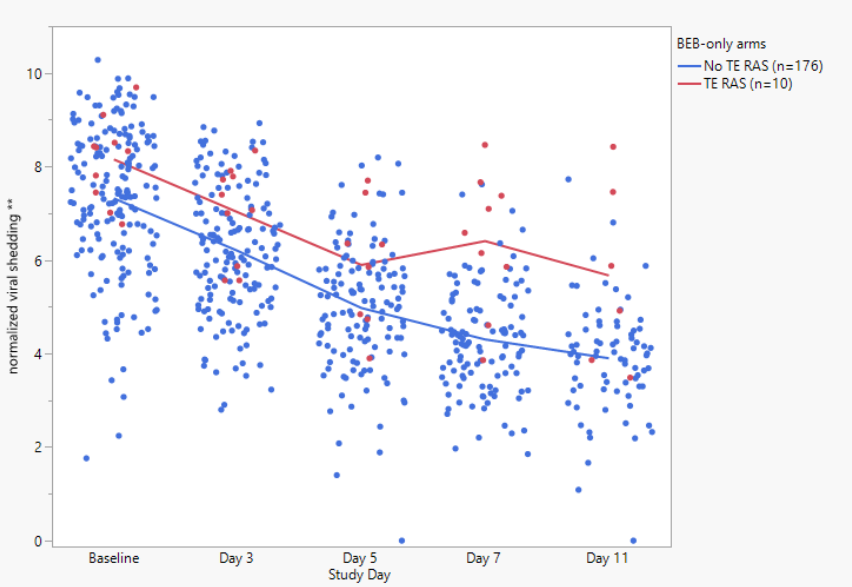
(b) (6)	BEB (LR)	V445G (7)	0.188	Delta (B.1.617.2-like)
	BEB (LR)	K444N (5)	0.452	Delta (B.1.617.2-like)
	BEB (LR)	G446V (7, 11), P499H (11)	0.277, 0.182, 0.705	Delta (B.1.617.2-like)
	BAM+ETE+BEB (LR)	G446V (7)	0.342	Delta (B.1.617.2-like)

BAM = bamlanivimab; BEB = bebtelovimab; ETE = etesevimab; HR = high-risk; LR = low-risk; RAS = resistance associated substitution

[a] Listed in order of substitutions and time points shown in column to the left

The virologic responses for subjects in whom TE RAS were detected are shown in Figure 6. In general, there was an association with higher viral shedding after Day 5 for subjects in whom TE RAS were detected compared with subjects with no TE RAS. With respect to clinical outcomes, no subjects with bebtelovimab TE RAS were hospitalized.

Figure 6: Mean Viral Shedding Over Time for Subjects in Whom Treatment-Emergent (TE) Resistance-Associated Substitutions (RAS) Were Detected Compared With Those With No TE RAS in Bebtelovimab-Only Arms of Trial PYAH (FDA analysis) *



BEB = bebtelovimab; RAS = resistance associated substitution; TE = treatment-emergent

* Only subjects with both baseline and post-baseline sequence data included (n=186 in bebtelovimab-only arms)

** Log_{10}-converted Ct values, using the formula: (45-CtNi)/(log_2 10) based on N1 (primary) and N2 (secondary) Ct values.

IX. Human Clinical Safety

The safety of bebtelovimab was evaluated in Trial PYAH in the phase 1 portion, Addendum 4, and the phase 2 portion, Arms 9 through 14. In Addendum 4, 24 participants were exposed to treatment and 10 participants received placebo. The cohorts in Addendum 4 were:

- Bebtelovimab 175 mg IV (140 mg/min), n=6
- Bebtelovimab 175 mg IV (350 mg/min), n=6
- Bebtelovimab 175 mg IV with bamlanivimab and etesevimab, n=6
- Bebtelovimab 1750 mg IV (350 mg/min), n=6
- Placebo, n=10

Data from Addendum 4 were not used for efficacy analyses but are included here to inform safety.

Treatment Arms 9-14 are described above in Section VIII, Human Clinical Efficacy.

The safety database for bebtelovimab is comprised of 602 participants who received bebtelovimab intravenously at the authorized dose or higher, alone or with bamlanivimab and etesevimab.

In Trial PYAH, participants received trial medication on Day 1 and were evaluated through Day 85 for clinical status and adverse events. Safety data from a database lock that occurred on August 27, 2021 was initially included with the EUA application. Following a request from FDA, Lilly provided additional safety information from the final database lock for Trial PYAH, when all participants had reached Day 85. As such, the data in this section are reflective of the final database lock that occurred on January 7, 2022.

Safety analyses for bebtelovimab are limited given that not all groups have a placebo control as a direct comparator. Additionally, the safety analyses could be confounded by health status as the placebo control group only included individuals who were low risk for progression to severe disease. Of the 602 participants who received bebtelovimab, either alone or with bamlanivimab or etesevimab, approximately 54% (n=326) were considered to be high risk for progression to severe disease, either due to age or due to the presence of a comorbidity (see Section VIII, Human Clinical Efficacy).

Clinical events related to COVID-19, including deaths and serious adverse events (SAEs), were exempt from adverse event (AE) reporting unless the investigator deemed the event was related to the administration of trial treatment or if the investigator deemed that the clinically significant laboratory findings or other abnormal safety assessments were more severe than expected for the participant's condition.

Adverse Events

Treatment-emergent adverse events (TEAEs) were slightly higher in the bebtelovimab groups compared to placebo. Most AEs were mild or moderate in severity and occurred at comparable rates across the treatment arms. There was a total of 7 (1%) SAEs and 1 death (<1%) in those who received bebtelovimab, with no SAEs or deaths in placebo (Table 15).

Table 15: Summary of Adverse Events in Participants Enrolled in Trial PYAH (Addendum 4 and Treatment Arms 9-14)

N (%)	Placebo (N = 138)	BEB (N = 243)	BAM + ETE + BEB (N = 359)	Total BEB (N = 602)
TEAEs	11 (8%)	34 (14%)	45 (13%)	79 (13%)
AEs by severity				
Mild	7 (5%)	17 (7%)	23 (6%)	40 (7%)
Moderate	4 (3%)	15 (6%)	16 (5%)	31 (5%)
Severe	0 (0%)	2 (1%)	6 (2%)	8 (1%)
Deaths due to AEs[a]	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
SAEs	0 (0%)	3 (1%)	5 (1%)	8 (1%)
DCs due to AEs (including death)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)

Abbreviations: AE = adverse events; BAM = bamlanivimab, BEB = bebtelovimab, BAM + ETE + BEB = bebtelovimab administered together with bamlanivimab and etesevimab, DC = discontinuation of study drug, ETE = etesevimab, PBO = placebo, SAE = serious adverse event, TEAE = treatment-emergent adverse event

[a]Death was initially reported as an SAE of hypoxia, then as a death due to COVID-19 and then updated to cerebrovascular accident after the interim database lock

Source: Regulatory Response: Additional Safety Information, Table 5.1.

Common adverse events reported in Trial PYAH included the preferred terms (PTs) nausea, vomiting, and rash. The incidence of these events was comparable across placebo and treatment arms and these events were, on the whole, generally rare (Table 16).

Table 16: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Occurring in ≥ 2 Participants Who Received Bebtelovimab in Trial PYAH (Addendum 4 and Treatment Arms 9-14)

SEE ATTACHED ADDENDUM

N (%)	Placebo (N = 138)	BEB (N = 243)	BAM + ETE + BEB (N = 359)	Total BEB (N = 602)
Infections and infestations	**2 (1%)**	**6 (3%)**	9 (3%)	**15 (3%)**
Pharyngitis streptococcal	0 (0%)	3 (1%)	0 (0%)	3 (1%)
Urinary tract infection	0 (0%)	1 (<1%)	2 (1%)	3 (1%)
Tonsillitis	0 (0%)	1 (<1%)	1 (<1%)	2 (0%)
Gastrointestinal disorders	**4 (3%)**	**4 (2%)**	**8 (2%)**	**12 (2%)**
Nausea	0 (0%)	1 (<1%)	4 (1%)	5 (1%)
Vomiting	1 (1%)	2 (1%)	2 (1%)	4 (1%)
Diarrhea	1 (1%)	0 (0%)	3 (1%)	3 (1%)
Investigations	**1 (1%)**	**6 (3%)**	**7 (2%)**	**13 (2%)**

Blood creatinine phosphokinase	0 (0%)	2 (1%)	1 (<1%)	3 (1%)
Blood phosphorus decreased	0 (0%)	2 (1%)	1 (<1%)	3 (1%)
Alanine aminotransferase	0 (0%)	0 (0%)	2 (1%)	2 (<1%)
Aspartate aminotransferase increased	0 (0%)	0 (0%)	2 (1%)	2 (<1%)
Blood lactate dehydrogenase increased	0 (0%)	1 (<1%)	1 (<1%)	2 (<1%)
C-reactive protein increased	0 (0%)	1 (<1%)	1 (<1%)	2 (<1%)
Skin and subcutaneous tissue disorders	**1 (1%)**	**4 (2%)**	**7 (2%)**	**11 (2%)**
Rash	1 (1%)	0 (0%)	4 (1%)	4 (1%)
Pruritus	0 (0%)	1 (<1%)	1 (<1%)	2 (<1%)
Nervous system disorders	**1 (1%)**	**5 (2%)**	**5 (1%)**	**10 (2%)**
Headache	0 (0%)	1 (<1%)	2 (1%)	3 (1%)
Presyncope	0 (0%)	1 (<1%)	1 (<1%)	2 (<1%)
Injury, poisoning and procedural complications	**3 (2%)**	**1 (<1%)**	**5 (1%)**	**6 (1%)**
Infusion related reaction	0 (0%)	0 (0%)	2 (1%)	2 (<1%)
General disorders and administration site conditions	**0 (0%)**	**2 (1%)**	**4 (1%)**	**6 (1%)**
Chest discomfort	0 (0%)	0 (0%)	2 (1%)	2 (<1%)
Vascular disorders	**0 (0%)**	**3 (1%)**	**2 (1%)**	**5 (1%)**
Hypertension	0 (0%)	2 (1%)	0 (0%)	2 (<1%)
Hypotension	0 (0%)	0 (0%)	2 (1%)	2 (<1%)
Blood and lymphatic system disorders	**0 (0%)**	**2 (1%)**	**2 (1%)**	**4 (1%)**
Leukopenia	0 (0%)	1 (<1%)	1 (<1%)	2 (<1%)
Psychiatric Disorders	**0 (0%)**	**2 (1%)**	**2 (1%)**	**4 (1%)**
Anxiety	0 (0%)	1 (<1%)	1 (<1%)	2 (<1%)
Cardiac disorders	**0 (0%)**	**0 (0%)**	**2 (1%)**	**2 (<1%)**
Atrial fibrillation	0 (0%)	0 (0%)	2 (1%)	2 (<1%)
Reproductive system and breast disorders	**0 (0%)**	**2 (1%)**	**0 (0%)**	**2 (<1%)**
Spontaneous penile erection[a]	0 (0%)	1 (1%)	0 (0%)	1 (<1%)
Intermenstrual bleeding[b]	0 (0%)	1 (1%)	0 (0%)	1 (<1%)
Pregnancy, puerperium, and perinatal conditions	**0 (0%)**	**0 (0%)**	**1 (<1%)**	**1 (<1%)**
Abortion spontaneous[b]	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)

Abbreviations: AE = adverse events; BAM = bamlanivimab, BEB = bebtelovimab, BAM + ETE + BEB = bebtelovimab administered together with bamlanivimab and etesevimab, PBO = placebo, TEAE = treatment-emergent adverse event
[a]Denominator adjusted because gender-specific for males: N = 63 (placebo), N = 116 (BEB), N = 156 (BAM + ETE + BEB)
[b]Denominator adjusted because gender-specific for females: N = 75 (placebo), N = 127 (BEB), N = 203 (BAM + ETE + BEB)
Source: Regulatory Response: Additional Safety Information, Table 5.2.

Moderate treatment-emergent AEs were rarely reported in patients who received bebtelovimab but were reported more commonly than in those who received placebo (Table 17). The only TEAE reported to be severe was an occurrence of spontaneous abortion, which is discussed below.

Table 17: Moderate Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Occurring in ≥ 2 Participants Who Received Bebtelovimab in Trial PYAH (Addendum 4 and Treatment Arms 9-14)

N (%)	Placebo (N = 138)	BEB (N = 243)	BAM + ETE + BEB (N = 359)	Total BEB (N = 602)
Subjects with ≥ 1	4 (3%)	15 (6%)	16 (5%)	31 (5%)
Infections and infestations	**1 (1%)**	**3 (1%)**	**4 (1%)**	**7 (1%)**
Urinary tract infection	0 (0%)	0 (0%)	2 (1%)	2 (<1%)
Skin and subcutaneous tissue disorders	**0 (0%)**	**1 (**<1**%)**	**5 (1%)**	**6 (1%)**
Rash	0 (0%)	0 (0%)	3 (0.8)	3 (1%)
Pruritus	0 (0%)	1 (<1%)	1 (<1%)	2 (<1%)
Vascular Disorders	**0 (0%)**	**1 (**<1**%)**	**2 (1%)**	**3 (1%)**
Hypotension	0 (0%)	0 (0%)	2 (1%)	2 (<1%)

Abbreviations: AE = adverse events; BAM = bamlanivimab, BEB = bebtelovimab, BAM + ETE + BEB = bebtelovimab administered together with bamlanivimab and etesevimab, PBO = placebo, TEAE = treatment-emergent adverse event
Source: Regulatory Response: Additional Safety Information, Table 5.3.

Deaths

As of the database lock on August 27, 2021, two deaths were reported. One death due to an AE was reported in a participant who received bebtelovimab alone (high risk, Treatment Arm 12). The participant was initially reported as hospitalized due to hypoxia and severe COVID-19 pneumonia the day after study drug administration. While the death was originally reported as due to COVID-19, the death was ultimately determined to be caused by cerebrovascular accident on Day 34. The investigator assessed the event of CVA as not related to open-label study treatment.

The other death occurred in an unvaccinated participant who received bebtelovimab with bamlanivimab and etesevimab (low risk, Treatment Arm 10). The death was due to COVID-19 and occurred on Day 5 post infusion. This participant was a 57 year old male with no relevant medical history of preexisting conditions reported. At screening, the participant SpO2 was greater than 93%. Prior to infusion, the participant's SpO2 was 93%. Post infusion, the SpO2 was reported to be 88-91% and the subject noted shortness of breath. Supplementary oxygen was provided to the patient and the patient was advised to go to the emergency room. The participant declined. On Days 2, 3, and 4, the participant was advised to go to the hospital, but declined on each day. On Day 5, the participant died of COVID-19 while en route to the hospital.

Serious Adverse Events

A total of 8 SAEs were reported in Trial PYAH. One occurred in a low risk participant (spontaneous abortion); the remainder of SAEs occurred in high risk participants. All SAEs

were not thought to be related to study treatment, with the exception of pulmonary embolism which was considered to be possibly related to study treatment.

In participants receiving bebtelovimab alone:

- Pulmonary embolism occurred on Day 18 in a 62 year old female.
- Cerebrovascular accident occurred in a 65 year old male. This patient was known to have COVID-19 pneumonia that developed following administration of trial medication.
- Meniscus injury occurred on Day 68 in a 40 year old female.

In participants receiving bebtelovimab with bamlanivimab and etesevimab:

- Osteomyelitis of the left great toe initially occurred on Day 2 in a 78 year old male who was hospitalized for a diabetic ulcer. Osteomyelitis was reported again on Day 49, and the SAE resolved with amputation of the toe.
- Lower limb fracture occurred on Day 7 in a 54 year old male. This participant required hospitalization on Day 14.
- Psychotic disorder occurred on Day 10 in a 39 year old female with a past history of anxiety and depression.
- Femur fracture occurred on Day 72 in an 89 year old female.
- Spontaneous abortion occurred in a 29 year old woman approximately 2 months after infusion.

In the case of the SAE of spontaneous abortion, the participant received bebtelovimab with bamlanivimab and etesevimab 25 days after her last menstrual period. The pregnancy was first detected with home testing but was then confirmed via blood sampling on Day 29. Approximately two months after infusion, the patient was reported to have had a spontaneous abortion at the gestational age of 8 weeks. No diagnostic tests were performed.

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes. It is unclear, however, whether the use of monoclonal antibodies augments or mitigates this risk. It is of note that no binding of clinical concern was detected in tissue cross reactivity studies using adult and fetal tissues with bebtelovimab, bamlanivimab, etesevimab, or other SARS-CoV-2 monoclonal antibodies authorized for emergency use. A risk summary for use of this therapeutic class is included in the Fact Sheet for Health Care Providers and acknowledges that there are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. While there are maternal and fetal risks associated with COVID-19 infection in pregnancy, it is unclear if treatment provides any benefit or risk to the developing fetus and that these products, including bebtelovimab, should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus (please see Section X, Specific Populations for more information).

Laboratory Findings

There were no clinically meaningful changes in hematology or clinical chemistries noted for any of the treatment arms.

Analysis of Submission-Specific Safety Issues

Hypersensitivity and Infusion-Related Reactions

Hypersensitivity and infusion-related reactions are known safety issues for intravenously-administered monoclonal antibodies. To identify potential infusion-related AEs, an analysis using narrow and broad terms within three SMQs (Anaphylactic Reaction, Angioedema, and Hypersensitivity) was completed by Eli Lilly. No cases of anaphylaxis were noted in Addendum 4 and in Treatment Arms 9-14. Hypersensitivity events were defined as immediate if they occurred within 24 hours of administration of trial medication or placebo. Six events (1%) were identified in those who received study drug, with no events occurring in those that received placebo. These events were considered mild or moderate. In those that received bebtelovimab (n=243), pruritus (n=1, 0.4%) and rash erythematous (n=1, 0.4%) were reported. In those who received bebtelovimab with bamlanivimab and etesevimab (n=359), pruritus (n=1, 0.3%), rash (n=1, 0.3%), and infusion-related reactions (n=2, 0.6%) were reported. For those with infusion related reactions, participants recovered with either interruption or withdrawal of the trial medication and did not require any additional intervention.

All nonimmediate hypersensitivity events, defined as events that occurred beyond 24-hours post-dose, were also considered mild or moderate. Ten events were reported (1.6%) for those who received study drug. In those that received bebtelovimab, urticaria (n=1, 0.4%) was reported. Rash (n=3, 0.8%), chest discomfort (n=2, 0.6%), hypotension (n=2, 0.6%) and drug hypersensitivity (n=1, 0.3%) were reported in those who receive bebtelovimab with bamlanivimab and etesevimab.

SEE ATTACHED ADDENDUM

In addition, rash was reported as a nonimmediate hypersensitivity event in a participant who received placebo.

Rash, pruritus, and infusion-related reactions are considered to be adverse reactions and are listed as such in the Fact Sheet for Health Care Providers. These events overall occurred at low rates within the safety database (infusion-related reactions, n=2, 0.3%; pruritus, n=2, 0.3%; rash and rash erythematous n=5, 0.8%).

Antiviral Resistance

In vitro resistance studies have identified spike RBD substitutions at positions K444, V445, G446, and P499 that confer reduced susceptibility to bebtelovimab. There is a potential risk of treatment failure if a patient is infected with a virus which has reduced susceptibility to bebtelovimab. Viral sequencing and phenotypic analyses are ongoing for clinical trial PYAH (BLAZE-4); baseline sequencing data were only available for 611 of the 702 subjects for whom nasal samples were collected in Arms 9 to 14 at the time of the virology database lock. There was only one instance of a subject in whom a baseline substitution with reduced susceptibility to bebtelovimab was detected, but the clinical significance of this is unclear.

Considering all substitutions detected at ≥15% allele fraction at positions K444, V445, G446, and P499 for Arms 9-14, 5.0% (10/199) of subjects treated with bebtelovimab alone harbored a variant that was treatment-emergent. This was more frequent than what was observed in the placebo arm (0%, 0/112), or when bebtelovimab was administered together with bamlanivimab and etesevimab (0.3%, 1/312). It is possible that these differences are related to sample size or the difference in selective pressure that is being placed on the virus (i.e. one antibody binding to one site versus three antibodies binding to three sites within the receptor binding

region of the S-protein). It is not known if treatment-emergent resistance would be more likely with other variants, such as Omicron; most participants in the trial were infected with Alpha (all three antibodies thought to have neutralizing activity) or Delta variants (bebtelovimab and etesevimab thought to have neutralizing activity).

The appearance of these treatment-emergent bebtelovimab resistance-associated substitutions was associated with higher viral loads in the subjects in whom they were detected, but none of these subjects were hospitalized. Despite this, there remains a theoretical risk that the emergence of treatment-resistant viral variants could lead to treatment failure and worse clinical outcomes.

The risk of resistance variants impacting clinical outcomes is not known and the assessment of resistance variants across the development program is ongoing. Because of the potential for emergence of resistant variants, it is recommended that patients treated with bebtelovimab 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.

For additional information related to antiviral resistance, please see Section VIII, Clinical Efficacy.

Immune Response Attenuation

Administration of bebtelovimab may attenuate the endogenous immune response to SARS-CoV-2 and potentially make patients more susceptible to re-infection. Similarly, bebtelovimab 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 COVID-19 vaccines in individuals who have received passive antibody therapy such as bebtelovimab. While there are limited data on the safety and efficacy of 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 on the estimated half-life of the available monoclonal antibodies used for therapy as well as the anticipated period of protection from reinfection.

Anti-Drug Antibodies

The Applicant submitted preliminary data to support validation of anti-drug antibody (ADA) assays, which remains under review at the time of authorization. All collected immunogenicity samples are appropriately stored for further analysis as indicated in Trial PYAH protocols. The ADA incidence and the effect of ADA after a single dose of bebtelovimab 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, bebtelovimab will be administered 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 bebtelovimab. The risk of ADE for bebtelovimab was addressed by the Applicant in non-clinical cell culture studies and 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. However, there was no clear evidence of enhanced disease in subjects treated bebtelovimab in Trial PYAH, or in other trials studying products within this therapeutic class.

X. Specific Populations

Pregnant and Breastfeeding Women

The emergency use of bebtelovimab is authorized for use in pregnant and breast feeding individuals.

As stated in the Fact Sheet for Health Care Providers, there are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Use of bebtelovimab in pregnant women has been limited; only one subject in PYAH reported pregnancy after administration of bebtelovimab together with bamlanivimab and etesevimab, and subsequently had a spontaneous miscarriage at 8 weeks gestation (see Section IX Clinical Safety).

The Fact Sheet for Health Care Providers recommends that bebtelovimab 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 bebtelovimab. In tissue cross reactivity studies using human fetal tissues, no binding of clinical concern was detected with bebtelovimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bebtelovimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bebtelovimab provides any treatment benefit or risk to the developing fetus.

Pregnancy is among the conditions that puts patients at high risk for clinical progression of COVID-19. The American College of Obstetricians and Gynecologists and the NIH support treatment of pregnant women with mild-to-moderate COVID-19 with monoclonal antibodies.[8,9] Recent publications have also described case series of pregnant women with mild-to-moderate COVID-19 who have been treated with other authorized monoclonal antibodies and reported treatment as well-tolerated and generally resulting in favorable outcomes.[10,11]

There are no available data on the presence of bebtelovimab 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 bebtelovimab and any potential adverse effects on the breastfed child from bebtelovimab 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.

Rationale for Inclusion of Adolescent Patients under EUA

[8] https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics. Accessed February 7, 2022
[9] https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed February 7, 2022
[10] Richley, M., et al. (2022). Neutralizing Monoclonal Antibodies for Coronavirus Disease 2019 (COVID-19) in Pregnancy: A Case Series. *Obstetrics & Gynecology*, 10-1097.
[11] Thilagar, B. P., et al. (2022). Anti-Spike Monoclonal Antibody Therapy in Pregnant Women With Mild-to-Moderate Coronavirus Disease 2019 (COVID-19). *Obstetrics & Gynecology*, 10-1097.

Since the beginning of the COVID-19 pandemic, over 11.4 million children have tested positive for COVID-19 in the United States, Puerto Rico, and Guam (https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/). Cases had dramatically increased during the Omicron variant surge, with over 3.5 million reported cases during January 2022 alone. While COVID-19 is typically milder in children, some pediatric patients require hospitalization and ICU-level care (Götzinger et al. 2020).

COVID-19 generally has a similar clinical course of disease in adolescents compared to adults and 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). Given the similarities in physiology to adults, and the similar PK in adolescents weighing ≥40 kg based on modeling, and the available adult clinical data, including the safety profile, there is prospect of benefit for this pediatric patient population.

Four adolescent patients received bebtelovimab, either alone or in combination with bamlanivimab and etesevimab, in Trial PYAH. However, based on the totality of evidence to support the prospect of benefit in adolescents, and that it is reasonable to believe the known and potential benefits outweigh the known and potential risks, the authorization of bebtelovimab includes adolescents who are 12 years of age and older and who weigh at least 40 kg.

Dosing Considerations for Special Populations

- Safety and pharmacokinetic (PK) data are not available in children, pregnant women, lactating women, patients with renal impairment, or patients with moderate or severe hepatic impairment.
- No dosage adjustment is recommended based on age, sex, body weight, baseline viral load, renal impairment, mild hepatic impairment, pregnancy, or lactation (see Section XI).
- Nonclinical reproductive toxicology studies with bebtelovimab have not been conducted.
- No binding of clinical concern was seen with bebtelovimab in a tissue cross-reactivity study in select human fetal tissues.
- No specific risks to pregnant or lactating women have been identified based on the nonclinical safety data.

XI. Human Clinical Pharmacology

Pharmacokinetics

- The Applicant submitted population PK data that included participants from treatment Arms 9, 10, 12, 13, and 14 of Study PYAH. In these five arms, participants received 175 mg single IV dose of bebtelovimab either alone (N=223) or in combination with 700 mg bamlanivimab and 1400 mg etesevimab (N=350). The summary of pharmacokinetic (PK) parameters from these five arms are provided by the Applicant and listed in Table 18. The current data suggest that the half-life of bebtelovimab is shorter than that of a conventional IgG monoclonal antibody. In response to FDA's Information Request, the Applicant stated that no clear attributes emerged as a potential cause of the observed half-life and noted that although 11.5 days is on the shorter end of the normal range, it falls within the range observed for other therapeutic antibodies.

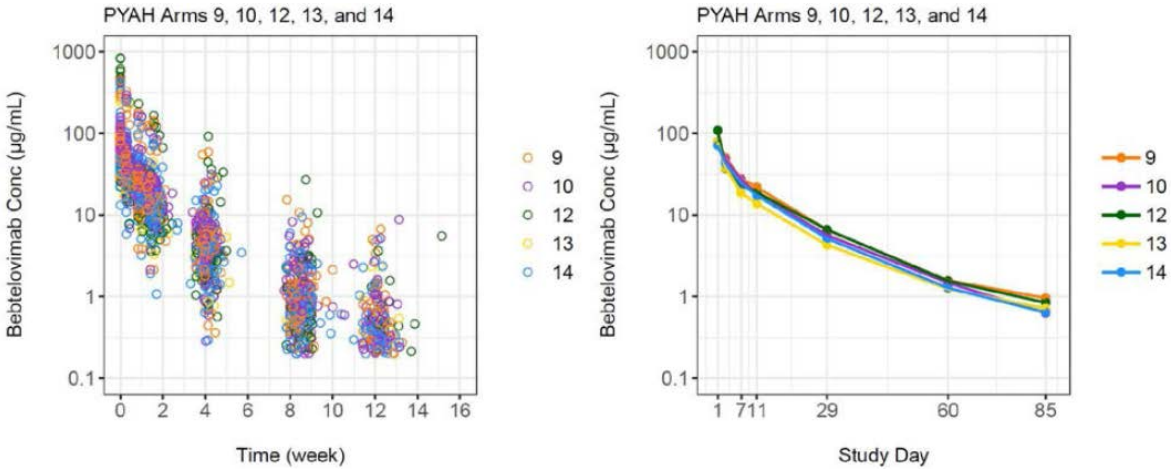
- In addition to these five arms, Study PYAH also included Arm A in Addendum 4, where low risk participants received a single IV dose of 70, 175, or 1750 mg bebtelovimab either alone or in combination with 700 mg bamlanivimab and 1400 mg etesevimab. Per the Applicant's summary of PK parameters at different dose levels, bebtelovimab serum concentrations are dose-proportional over the range of 70 to 1750 mg IV dose.
- Bebtelovimab concentration-time profiles following administration of bebtelovimab alone or in combination with bamlanivimab and etesevimab are similar in both low-risk and high-risk populations, as shown in Figure 7**.**
- Serum bebtelovimab PK samples were analyzed using a LC/MS/MS method.

Table 18: Summary of Bebtelovimab PK Parameters Following an IV dose of 175 mg (N=573) in Study PYAH Arms 9, 10, 12, 13, and 14

Parameter	Geometric Mean (CV%)
CL (L/d)	0.335 (39.3%)
V_{SS} (L)	4.61 (25.3%)
$t_{1/2}$ (d)	11.5 (25%)
C_{max} (µg/mL)	59.8 (30.1%)
CD_{29} (µg/mL)	4.35 (69.8%)
AUC (µg*d/mL)	522 (39.3%)

Information source: Applicant's Emergency Use Authorization request
AUC = area under the curve from 0 to infinity; CL = systemic clearance; CD_{29} = concentration at Day 29; C_{max} = maximum concentration; CV = coefficient of variation; V_{ss} = steady-state volume of distribution; $t_{1/2}$ = terminal phase half-life
Note: C_{max}, CD_{29}, and AUC were generated using bebtelovimab population PK model and participant post hoc parameters.

Figure 7: Individual (left) and Mean (right) Observed Bebtelovimab Concentration-Time Data Following 175 mg Alone (Arms 9 and 12) or in Combination (Arms 10, 13, and 14) with 700 mg Bamlanivimab and 1400 mg Etesevimab to Low (Arms 9 and 10) and High (Arms 12, 13, and 14) Risk Participants



Source: Applicant's bebtelovimab population PK and PK/PD interim report of Study PYAH Arms 9 to 14 Data

Pharmacodynamics and Pharmacodynamic Modeling and Simulation

The Applicant's PD model and their conclusions based on the model have not yet been fully evaluated in detail by the Agency. However, this information is included for descriptive purporses as the Applicant's considerations are pertinent towards their evaluated dose and the proposed dose for the EUA.

Based on pharmacodynamic (PD) (viral load) data from Study PYAH Arms 9 to 14, the Applicant drew the following conclusions:

- Significant overall treatment effects in reduction in viral load were observed in the bebtelovimab monotherapy and the combination therapy, relative to placebo.
- The reduction in viral load for bebtelovimab administered alone was similar to that when bebtelovimab was co-administered with bamlanivimab and etesevimab.
- The magnitude of reduction in viral load in this study was similar to that seen with in phase 3 cohorts of the BLAZE-1 and BLAZE-4 studies for bamlanivimab and etesevimab.

Using these viral load data and PK data from Study PYAH Arms 9, 10, 12, 13, and 14, the Applicant developed a target-cell mediated viral PD model. This PD model is similar to the ones that the applicant has previously submitted to support other EUAs (EUA 90 and EUA 94). Based on bebtelovimab's PD model and simulation, the Applicant submitted the following statement:

- The model adequately described and predicted the observed data.
- The simulation results suggested that the treatment effect is expected to be greater for patients who are treated earlier during the course of the disease.
- Covariates of pharmacodynamic effect were age (decreasing viral clearance with increasing age), the Delta variant, and the Alpha variant (lower viral clearance in the presence of Delta or Alpha). However, these covariates applied to all study arms (placebo and treatment) and were not significant on the actual drug effect (clinical outcome).

Of note, the Applicant acknowledged that an E_{max} model cannot be used for bebtelovimab due to the limited information for concentration-response and thus a simple treatment effect model was used. Therefore, in *vivo* EC_{90} of bebtelovimab cannot be determined using this PD model to support the dose selection.

Rationale for Dose Recommendation

The Applicant stated that a single dose of 175 mg bebtelovimab will achieve serum bebtelovimab concentrations above the targeted bebtelovimab effective serum concentration (1.43 to 1.92 µg/mL) for at least 28 days in at least 90% patients after drug administration. The Applicant's derived targeted bebtelovimab effective serum concentration was based on the following information:

- The *in vivo* serum target concentration of bebtelovimab proposed by the Applicant is mainly based on the potency comparison between bebtelovimab and bamlanivimab. *In vitro* pseudovirus neutralization experiments show that bebtelovimab is roughly 2.2 times as potent as bamlanivimab, which has an *in vivo* EC_{90} of 4.20 (95% CI: 3.2; 4.3) µg/mL

determined by the Applicant's PK-viral dynamic model (based on data from clinical dose ranging study).[12]

- *In vitro* authentic virus neutralization studies showed there is no fold change in potency of bebtelovimab against the Omicron variant compared to other variants including the Delta variant.

Of note, the Applicant's proposed *in vivo* effective serum concentration (1.43 to 1.92 µg/mL) of bebtelovimab is expected to be higher than a range of potential *in vivo* EC_{90} values that were determined based on *in vitro* authentic virus neutralization potency of bebtelovimab (Tables 19 and 20), as well as an estimated lung-to-serum concentration ratio of 5% (lower end of reported lung to serum distribution ratios) for IgG monoclonal antibodies. Therefore, the Applicant's targeted bebtelovimab effective serum concentration (1.43 to 1.92 µg/mL) is regarded as conservative. After a single-dose administration of 175 mg bebtelovimab, as shown in the Figure 8, bebtelovimab concentrations in more than 90% patients of Arms 9, 10, 12, 13, and 14 in Study PYAH were well above 1.92 µg/mL for more than 11 days.

Moreover, as supported by the clinical virology data from Study PYAH, 175 mg bebtelovimab alone and in combination with bamlanivimab and etesevimab achieved comparable levels of viral load reduction in both lowrisk and high risk patients.

Table 19: Authentic SARS-CoV-2 Plaque Reduction Neutralization Titer of Spike Variants Present in Circulation by Bebtelovimab

Viral Lineage	Viral Isolate/Construct	BEB		
		EC_{50} ng/mL (CI 95%) [a]	EC_{90} ng/mL (CI 95%) [a]	Fold Change [b]
WT comparator	rWA1 Strain	15 (13-16)	56 (46-69)	NA
Iota	rWA1 + E484K	10 (9-11)	47 (40-56)	0.67
Multiple Lineages	rWA1 + E484Q	14 (12-16)	67 (50-91)	0.93
WT comparator	rWA1 Strain	9 (8-10)	33 (26-43)	NA
Epsilon	rWA1 + L452R	8 (7-10)	52 (32-83)	0.89
WT comparator	WA1/2020 isolate	11 (8-17)	108 (48-241)	NA
Alpha	B.1.1.7 isolate	4 (3-4)	44 (29-67)	0.36
Beta	B.1.351 isolate	7 (5-10)	45 (23-87)	0.63
WT comparator	WA1/2020 isolate	10 (8–12)	59 (37–94)	NA
Delta	B.1.617.2 isolate	8 (7–9)	35 (29–44)	0.8

Source: Applicant's Emergency Use Authorization request
BEB = bebtelovimab (LY3853113); CI = confidence interval; EC_{50} = concentration inhibiting maximal activity by 50%; EC_{90} = concentration inhibiting maximal activity by 90%; NA = not applicable; r = recombinant; WA = Washington; WT = wild type.
a Absolute EC_{50} and EC_{90} values presented are a result of a single experiment.
b Fold shifts are calculated comparing the EC_{50} of the variant to that of the respective WA1 comparator that was performed within the same assay.

Table 20: Authentic SARS-CoV-2 Cytopathic Effect Inhibition of Spike Variants By Bebtelovimab and Different Combinations of Bebtelovimab With Bamlanivimab and Etesevimab

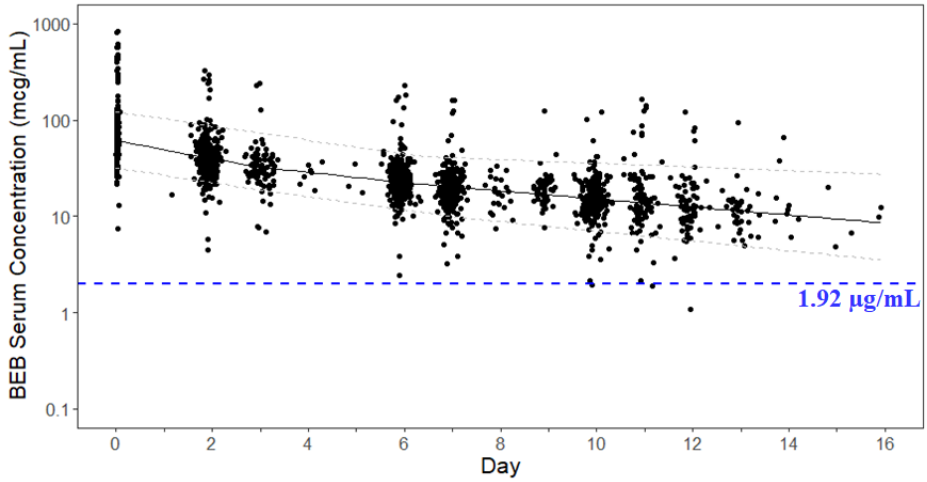
Viral Variant	WA1 strain	B.1.617.2 (Delta)		B.1.1.529 (Omicron)	
	$EC_{>99}$ ng/mL [a]	$EC_{>99}$ ng/mL [a]	Fold Change [b]	$EC_{>99}$ ng/mL [a]	Fold Change [b]

[12] Chigutsa, E., et al. (2021). Population Pharmacokinetics and Pharmacodynamics of the Neutralizing Antibodies Bamlanivimab and Etesevimab in Patients With Mild-to-moderate COVID-19 Infection. *Clinical Pharmacology & Therapeutics*. 10-1002

BEB	3.66	4.88	1.3	< 2.44 [c]	< 0.67 [c]
BEB+BAM	3.66	7.32	2	3.66	1
BEB+ETE	14.65	< 2.44 [c]	< 0.17 [c]	14.65	1
BEB+BAM+ETE	7.32	4.88	0.67	9.77	1.3

Source: Applicant's response to an information request
BAM = bamlanivimab; BEB = bebtelovimab; ETE = etesevimab; EC_{99} = concentration inhibiting maximal activity by 99%; WA = Washington; NA = not applicable
a $EC_{>99}$ values presented are a result of a single experiment with technical replicates.
c Values of < 2.44 were given when an antibody showed full neutralization even at the lowest concentration tested, fold shifts for these values were calculated using 2.44 as the $EC_{>99}$.

Figure 8: Bebtelovimab Serum Concentration Profile of All Participants in Study PYAH Arms 9, 10, 12, 13, and 14



Source: Reviewer's analysis using concentration data from Study PYAH Arms 9, 10, 12, 13, and 14. BEB = bebtelovimab
Black dots: observed bebtelovimab concentration data; Blue dotted line: concentration value at 1.92 µg/mL; Black solid line: median observation; Black dashed lines: 5th (upper) and 95th (lower) percentiles of observations.

Overall, the Agency concurs with the proposed single-dose regimen of 175 mg bebtelovimab administered as a single IV infusion for this EUA request. However, the Agency recognizes the current rationale for the dosing regimen has the following limitations:

- The *in vivo* target concentration used by the Applicant was primarily based on the comparison of potency between bebtelovimab and bamlanivimab and not based on any clinical virology data or clinical outcome data with bebtelovimab.
- Only one dose level of bebtelovimab 175 mg was evaluated. Therefore, a dose-response relationship cannot be determined to predict a potential optimal dose of bebtelovimab with a maximum effect of viral load reduction.
- Additionally, there lacks clinical virology or outcome data as a proof-of-concept for the anti-Omicron activity of bebtelovimab observed in nonclinical settings, further complicating determination of minimum or optimal efficacious concentration of bebtelovimab against the Omicron variant.

Rationale for Dosing Recommendations in Pediatric Patients and Other Specific Populations

Bebtelovimab is a monoclonal antibody that is expected to be eliminated via proteolytic degradation to amino acids. Bebtelovimab is not anticipated to be eliminated intact in the urine nor metabolized by cytochrome P450 enzymes in the liver. Renal impairment is not expected

to affect the PK of bebtelovimab. Based on population PK and covariant analysis, the Applicant had the following findings:

- Age, sex, race, baseline viral load level, and mild hepatic impairment did not affect the PK of bebtelovimab. The Applicant claimed that moderate hepatic impairment did not affect the PK of bebtelovimab, but it is inconclusive due to the limited number of subjects with moderate hepatic impairment in the popPK analysis (n=2).
- While body weight was a covariate on clearance and volume of distribution of bebtelovimab, the impact of the change in exposure was not clinically meaningful, for example, in reduction in viral load.

Based on population PK modeling and simulation, the Applicant predicted that bebtelovimab concentrations in adolescents (weighing at least 40 kg) will be similar to those in adults, as shown in Table 21.

Table 21: Bebtelovimab Exposure Parameters in Adults And Adolescents Weighing At Least 40 kg Following Administration of 175 mg Bebtelovimab

	Adults (N = 1000)			Adolescents ≥40 kg (N = 815)		
Parameter	**Median**	**5th Percentile**	**95th Percentile**	**Median**	**5th Percentile**	**95th Percentile**
C_{max} (µg/mL)	62.4	35.7	118	79.6	38.8	150
C_{D29} (µg/mL)	4.70	1.56	11.3	5.10	1.31	13.1
AUC (µg·d/mL)	548	308	1000	643	321	1180

Source: Applicant's Emergency Use Authorization request

Taken together, the Agency agrees no dose adjustment is warranted based on body weight or other intrinsic patient factors.

Drug-Drug Interactions

Bebtelovimab is 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

- A 3-week nonclinical intravenous toxicology study with bebtelovimab was conducted in Sprague Dawley rats.
- No findings of significant clinical concern were noted at up to the highest dose tested in rats (at approximately 140 times the authorized human dose).
- Non-adverse findings in rats administered bebtelovimab subcutaneously for 3 weeks included:
  - Minimal decreases in hemoglobin, hematocrit, and red blood cell count in males
  - Minimal increases in reticulocyte counts in males and females
  - Moderate decreases in platelet counts in males and females
  - These findings were not observed after recovery and occurred in the absence of histopathological changes and so were considered non-adverse. Bebtelovimab is authorized to be administered by the intravenous route only. Thus, the clinical relevance

of these non-adverse findings noted in animals exposed via the subcutaneous route are unclear.

- GLP tissue cross-reactivity studies were conducted with bebtelovimab using normal adult human, human fetal, monkey and rat tissues. No binding of clinical concern was observed.
- Single dose PK studies with bebtelovimab were conducted in Sprague Dawley rats and cynomolgus monkeys. Clearance rate of bebtelovimab was similar between both species (0.20 ml/hr/kg); and the systemic exposure, $AUC_{0\text{-}inf}$, were about 5000 µg*hr/mL in rats and monkeys.

XIII. Nonclinical Data to Support Efficacy

- Bebtelovimab was assessed in non-clinical studies of epitope mapping, binding, neutralization, effector function, resistance, and antibody-dependent enhancement (ADE) of infection. Bebtelovimab was also assessed for activity in a hamster model of SARS-CoV-2 infection and for ADE in an African green monkey model.

- Bebtelovimab binds to the SARS-CoV-2 S-protein, with an affinity (K_D) of 74.5 pM. The binding epitope of bebtelovimab is located within the RBD of the S-protein. Binding studies demonstrated that bebtelovimab competes directly with the cellular receptor ACE2 and inhibits ACE2 binding to the S-protein RBD with an IC_{50} value of 0.38 nM (56 ng/mL).

- Analysis of the X-ray crystallography-determined 3-dimensional structure of the bebtelovimab:RBD complex indicated that the amino-acid positions in the RBD that are structurally located within 5 Å of bebtelovimab are: T345, R346, N439, N440, L441, S443, K444, V445, G446, G447, N448, Y449, N450, Q498, P499, T500, N501, G502, V503, Q506, R509. Most of these amino acids have >99% conservation, but 5 positions are less conserved: R346 (98.900%), N440 (97.266%), G446 (97.393%), Q498 (97.418%) and N501 (75.473%) (source: cov.lanl.gov, accessed 01/26/2022).

- The effector function of bebtelovimab, including Fc and complement (C1q) receptor binding activity, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP), were assessed. Bebtelovimab demonstrated binding to human Fc gamma receptors (FcγRs) FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa and complement component C1q. Consistent with the binding data, bebtelovimab demonstrated FcγRIIIa activity (ADCC activity) on reporter cells upon engagement by S-protein on CHO-Spike/hCD20 target cells. While bebtelovimab binds C1q by ELISA, CDC activity was not observed in cell-based assays. In ADCP assays, bebtelovimab mediated ADCP activity in macrophages from 2 of 3 donors in the macrophage/CHOSpike/hCD20 co-culture.

- ADE of SARS-CoV-2 infection was evaluated in cell culture. Bebtelovimab alone and in combination with bamlanivimab and/or etesevimab did not mediate productive ADE in Raji, THP-1, ST486 or primary macrophage cells. Assuming an EC_{50} value for bebtelovimab of approximately 0.042 nM (6 ng/mL), there was no evidence of ADE at concentrations up to 60,000-fold below the EC_{50} value.

- The cell culture neutralization activity of bebtelovimab against SARS-CoV-2 was measured in a dose-response model quantifying plaque reduction using cultured Vero E6 cells.

Bebtelovimab neutralized the USA/WA/1/2020 isolate of SARS-CoV-2 with an estimated EC_{50} value = 0.044 nM (6.4 ng/mL).

- Cell culture passage studies of SARS-CoV-2 in the presence of bebtelovimab to select for resistance are ongoing. Selection studies using yeast display identified substitutions with reduced susceptibility to bebtelovimab of K444T, V445A and P499R; additional substitutions requiring 2 nucleotide changes were identified at position G446. All possible substitutions from single nucleotide changes at these positions identified the following substitutions and fold-reductions in susceptibility to bebtelovimab in ACE-2 binding inhibition experiments: K444E/N/T/Q (>74-fold / >72-fold / >76-fold / 17.5-fold), V445A/D/F/G (17-fold / >72-fold / 42.6-fold / >72-fold), G446D/V (7-fold / 4.2-fold) and P499H/R (>74-fold / >76-fold). Substitutions evaluated in pseudotyped virus-like particle (VLP) assays which conferred reduced susceptibility to bebtelovimab included: K444N (>1,901-fold), K444Q (208-fold), K444T (>1,814-fold), V445A (111-fold), V445F (369-fold), V445G (>730-fold), G446D (69.4-fold), G446V (8.2-fold), P499H (>1,606-fold), P499R (>1,870-fold) and P499S (25.3-fold). In the context of Delta spike protein, G446V substitution had reduced susceptibility of 16.4-fold. Note that, given the difference in sensitivity between the binding and pseudotyped VLP assays, other substitutions at these positions may be clinically meaningful.

- In pseudotyped VLP assays of substitutions identified as causing reduced susceptibility to other authorized mAbs, bebtelovimab retained activity (<5-fold change) against the following substitutions: D405G, Q409E, K417E/N/T, D420N, N439K, N440D/K, L452R, T453F, L455F, N460K/S/T, A475V, V483A, E484D/K/Q, F486I/V, Y489H, F490S, Q493K/R and S494P.

- The cell culture neutralization activity of bebtelovimab against current and previous variants of concern has been evaluated in both pseudotyped VLP and authentic virus assays. In pseudotyped VLP assays, bebtelovimab had an EC_{50} value against the Wuhan-Hu-1 spike protein of 0.014 nM (2 ng/mL). Compared with this control spike protein, bebtelovimab retained neutralization activity (<5-fold reduction) against full-length spike protein from the following WHO-designated lineages: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Delta [+K417N] (AY.1/AY.2), Epsilon (B.1.427/B.1.429), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37), Omicron (B.1.1.529/BA.1), Omicron [+R346K] (BA.1.1) and Omicron (BA.2). The Mu (B.1.621) variant showed a reduction in susceptibility to bebtelovimab of 5.3-fold.

- In authentic virus assays, bebtelovimab retained activity (<5-fold reduction) against the following lineages in plaque assays: Alpha (B.1.1.7), Beta (B.1.351) and Delta (B.1.617.2/AY.3). Using recombinant SARS-CoV-2, bebtelovimab retained activity against the following key substitutions found in other lineages L452R (Epsilon), E484K (Iota and other lineages), E484Q (multiple lineages). Bebtelovimab was also active against Omicron (B.1.1.529/BA.1) in a cytopathic effect (CPE) assay; EC_{50} values were not determined for this assay.

- The antiviral activity of bebtelovimab alone and administered together with bamlanivimab and/or etesevimab was tested in a Syrian hamster SARS-CoV-2 prophylaxis model. Hamsters (n=5 to 8 per group) were administered antibody (control IgG, bebtelovimab, bamlanivimab, etesevimab) by the intraperitoneal route on Day -1 and were challenged

with 1.1×10^5 $TCID_{50}$ SARS-CoV-2 (USA-WA1/2020) on Day 0. Bebtelovimab had dose-dependent changes in body weight, lung weight (as percent of body weight), viral load in lung tissue, and viral replication based on sub-genomic viral RNA levels in lung tissue. Significant differences in these endpoints compared with control animals was observed at 0.25 and 2.5 mg/kg dose levels of bebtelovimab. Combinations of bebtelovimab with bamlanivimab and etesevimab also demonstrated dose-dependent changes in study endpoints.

- The potential for ADE of infection was studied on the African green monkey (AGM) model of SARS-CoV-2 infection. Naive adult male and female AGMs were assigned to low-, mid-, and high-dose groups of bebtelovimab, bebtelovimab together with bamlanivimab and etesevimab, or a nonspecific IgG1 control. On Study Day 0, animals were inoculated with 3 x 10^6 $TCID_{50}$ of SARS-CoV-2 (SARS-CoV-2 isolate USA WA1/2020), with dose administrations divided between the intratracheal and intranasal routes. Bebtelovimab doses were 0.01 (low sub-neutralizing), 1 (mid), and 5 (neutralizing) mg/kg. Combination dose groups were 0.01/0.04/0.08 (sub-neutralizing) or 5/20/40 mg/kg of bebtelovimab, bamlanivimab, and etesevimab, respectively. There were significant ($q<0.05$ in throat, BALF or $p<0.05$ in lung) reductions in viral genomes and replicating virus (sub-genomic RNA) in the throat and lungs of the 1- and 5-mg/kg BEB, and 5/20/40-mg/kg bebtelovimab/bamlanivimab/etesevimab dosing groups. Significant ($q<0.05$) reduction in viral genomes was also observed in the bronchioalveolar lavage of the 5 mg/kg bebtelovimab dose group. Overall, there was no evidence that treatment with bebtelovimab, alone or administered together with bamlanivimab and etesevimab caused ADE of infection, based on viral RNA levels in nose, throat, BALF, lung tissue and blood.

XIV. Supply Information

Bebtelovimab is available in single use vials containing bebtelovimab 175 mg/2 mL per vial. Each dose requires one vial of bebtelovimab. The current supply projections for bebtelovimab is summarized in Table 22.

Table 22: Supply Projections for the Next 2 Months

Vials/Doses	Earliest Supply availability
	(b) (4)

XV. Chemistry, Manufacturing, and Controls Information

- Bebtelovimab is a recombinant neutralizing human immunoglobulin G-1 (IgG1 variant) monoclonal antibody (molecular weight of 144 kDa) consisting of 2 identical light chain polypeptides composed of 215 amino acids each and 2 identical heavy chain polypeptides composed of 449 amino acids produced in a Chinese Hamster Ovary (CHO) cell line. Bebtelovimab was designed to target the spike protein of SARS-CoV-2 and thereby block the virus attachment to human angiotensin-converting enzyme 2 (ACE2) receptors, preventing subsequent viral entry into human cells and viral replication and decrease viral shedding and transmission. Bebtelovimab binds an epitope of spike protein within the

receptor-binding domain (RBD) that is distinct from those bound by bamlanivimab and etesevimab. Bebtelovimab also exhibits antibody-dependent cell-mediated cytotoxicity (ADCC) activity. SEE ATTACHED ADDENDUM

- Bebtelovimab Injection, 170 mg/2 mL vial, is a sterile solution formulated in an (b) (6) at pH (b) (6), consisting of (b) (6) histidine (b) (6), 50 mM sodium chloride, 6.0% sucrose, 0.05% w/v polysorbate 80, and water for injection.

- IND 154936 was referenced for this EUA and contains the supporting CMC data. The data submitted in IND 154936 support the conclusion that the manufacture of bebtelovimab is sufficiently controlled and leads to a product that is suitable for use under EUA.

- Changes in drug substance included scale up. Several drug product manufacturing changes were made during development of bebtelovimab, including changes in 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. SEE ATTACHED ADDENDUM

- The requested expiration dating period of 12 months at 2°C to 8°C for drug product is supported by a risk assessment of the available drug product stability data including 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. In these studies, the 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 154936 with additional stability data from ongoing studies to further support the proposed 12-month dating period.

- The available in-use compatibility data support the proposed clinical procedures for preparation, handling, storage, and administration.

- Data supporting any additional manufacturing changes for bebtelovimab drug substance and drug product intended for this EUA will be submitted to IND 154936 prior to use. These data will be reviewed in a timely manner to allow rapid use of product under the EUA.

XVI. Manufacturing Site Inspections

Table 23: Manufacturing Sites SEE ATTACHED ADDENDUM

Manufacturing Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	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	03/16/2021	Acceptable
(b) (4)	Drug substance and drug product manufacturing, and in-	(b) (4)	(b) (4)	Acceptable

	process, release, and stability testing			
(b) (4)	Drug substance and drug product release/stability testing	(b) (4)	(b) (4)	Acceptable
(b) (4)	Adventitious virus testing of (b) (4)	(b) (4)	(b) (4)	Acceptable
(b) (4)	Drug product packaging and labeling	(b) (4)	(b) (4)	Acceptable

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following conditions to the authorization as necessary to protect the public health[13]:

- The Sponsor will manufacture bebtelovimab to meet all quality standards and per the manufacturing process and control strategy as detailed in the Sponsor's EUA request. The Sponsor will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

- All manufacturing, packaging, and testing facilities for both drug substance and drug product used for EUA supply will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).

- The Sponsor will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of bebtelovimab that includes the following:
  - Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
  - Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications.

  If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

  The Sponsor will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, the Sponsor must recall them.

[13]See the evaluation documented in OMQ's Authorization Recommendation Memo for Emergency Use Authorization in CMS Case #625508, as well as OPQ's Chemistry, Manufacturing, and Controls EUA Assessment Memo, dated February 11, 2022, associated with EUA 111.

If not included in its initial notification, the Sponsor must submit information confirming that the Sponsor has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. The Sponsor must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- The Sponsor will list bebtelovimab with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

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

- The NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov/; updated February 1, 2022) reviews various treatments for COVID-19 and the associated available evidence. For nonhospitalized patients who are at high risk of progressing to severe COVID-19, the COVID-19 Treatment Guidelines Panel recommends the following treatments, listed in the order of preference based on efficacy and convenience of use:
    - Ritonavir-boosted nirmatrelvir (Paxlovid™)
    - Sotrovimab
    - Remdesivir
    - Molnupiravir
- 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 January 12, 2022) also suggests the use of ritonavir-boosted nirmatrelvir (Paxlovid™), remdesivir, molnupiravir, and SARS-CoV-2 monoclonal antibody therapies for the treatment of patients with mild-to-moderate COVID-19 at high risk of progression to severe disease.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Bebtelovimab is a recombinant neutralizing human IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. Bebtelovimab is administered as a single IV administration over 30 seconds.
Bebtelovimab has demonstrated broad neutralizing capability in cell culture, including against the Omicron variant, and has shown to be active in animal models against SARS-CoV-2.

The primary clinical data to support the authorization of bebtelovimab for the treatment of mild-to-moderate COVID-19 was generated from Trial J2X-MC-PYAH (PYAH; BLAZE-4), a double-blind, randomized, single-dose trial in participants with mild-to-moderate COVID-19 illness conducted under IND 150440. This trial studied bebtelovimab alone and administered together with bamlanivimab and etesevimab in Addendum 4 and in Arms 9-14. Addendum 4 was the phase 1, placebo-controlled, single ascending dose portion of the trial that enrolled

low risk participants with mild-to-moderate COVID-19. Arms 9-14 was the phase 2 portion of the trial, enrolling both low and high risk participants with mild-to-moderate COVID-19. Based on our review of available data, it is reasonable to believe that bebtelovimab "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 progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. The known and potential benefits of bebtelovimab outweigh the known and potential risks for the proposed authorized use.

The predefined primary endpoint for Treatment Arms 9-11 (low risk participants) was proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (a metric also known as persistently high viral load, PHVL). Statistical significance was not achieved with bebtelovimab alone, nor with bebtelovimab administered with bamlanivimab and etesevimab. Bebtelovimab alone and bebtelovimab with bamlanivimab and etesevimab reduced viral load on Day 5 relative to placebo (nominal p-value <0.05). As discussed above, PHVL and change in viral load have not been shown to be surrogates of clinical benefit based on FDA analyses of data generated following the study of other antibodies in previous trials conducted both by Eli Lilly as well as by other sponsors. In addition, these analyses used data generated from clinical trials conducted prior to the emergence of the Omicron variant and because current hospitalization and death rates might differ, it is unclear how these factors could affect our assessment of these virologic endpoints as surrogates for clinical outcomes. Changes in viral load have been used as supportive evidence to demonstrate activity of COVID-19 therapeutics, including neutralizing monoclonal antibodies, and as such, changes in viral load are being considered as supportive evidence for the authorization of bebtelovimab.

When considering other secondary endpoints, bebtelovimab shortened time to sustained symptom resolution compared to placebo to a statistically significant degree. Because of the lack of significant results of the primary endpoint, the p-values for this secondary endpoint should be interpreted with caution given the lack of type I error control. However, the two day difference observed is also likely to have clinical significance, and is also supportive of the overall activity of bebtelovimab. While a difference was not appreciated in the rate of COVID-19 related hospitalization or death in bebtelovimab treated groups compared to placebo, this trial was not powered to see differences in this outcome in participants who are considered to be low risk for progression to severe COVID-19.

Due to the availability of treatments authorized for emergency use for patients with mild-to-moderate COVID-19 and risk factors for progression to severe COVID-19 at the time that Trial PYAH was conducted, participants in Treatment Arms 12-13 and 14 were studied without a placebo control due to lack of equipoise. Further complicating these analyses, Treatment Arms 12 and 13 occurred concurrently while Treatment Arm 14 was subsequently opened after complete enrollment of Arms 12 and 13, and was not randomized. Efficacy analyses for bebtelovimab are therefore limited and are mostly descriptive. As stated in Section VIII, a reduction in viral load was appreciated in those who received bebtelovimab, and the time to sustained symptom resolution was comparable to what was seen in the placebo-controlled treatment arms that enrolled low risk participants. The proportion of participants who experienced COVID-19 related hospitalization and death by Day 29 was 1.7 to 4% in Treatment Arms 12-14. Unfortunately however, interpretation of these data is limited by the lack of placebo control in these high risk treatment arms. In prior monoclonal antibody trials

that enrolled high risk patients, the typical rates of hospitalization or death for the placebo group were 3-7%. However, comparisons to these data are limited as these trials occurred when different viral variants were circulating and baseline factors, such as age, other demographics, and seropositivity rates, varied.

It is of note that the data from Trial PYAH were generated during a time when the Omicron variant (B.1.1.529/BA.1) was not circulating in the United States. No subject in Trial PYAH was infected with virus of the Omicron lineage or sub-lineages and the majority of participants in the trial were infected with Delta (49.8%) and Alpha (28.6%). It is unknown whether clinical outcomes seen in Trial PYAH would be similar if conducted during Omicron. It is also unclear if a reduction in COVID-19 related hospitalization and death by Day 29 in a high risk population would be appreciated at a similar rate to what was seen with other authorized monoclonal antibodies, if a placebo was utilized as a control comparator. However, such data are also unavailable for other authorized or approved products as they were also studied prior to emergence of Omicron.

Despite these deficiencies, based on the totality of scientific evidence available, including the available phase 2 and pharmacokinetic data, along with the nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab may be effective for the treatment of patients with mild-to-moderate COVID-19. In addition, the mechanism of action for bebtelovimab is similar to other neutralizing SARS-CoV-2 monoclonal antibodies, including bamlanivimab and etesevimab, that have demonstrated clinical efficacy in patients infected with other SARS-CoV-2 variants and who are at high risk of COVID-19 progression. Because of these uncertainties however, as well as the limitations in the efficacy analyses described above, the authorization for bebtelovimab is specifically limited to patients for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate, beyond the other required components of the authorization (for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death). Recognizing the limitations of the available clinical data, conditions to the letter of authorization require Lilly to provide a protocol proposal by March 1, 2022, to obtain additional data for the treatment of mild-to-moderate COVID-19 in non-hospitalized participants. Following FDA request, Lilly has also agreed to submit a proposed protocol to evaluate PK and safety in pediatric patients less than or equal to 12 years of age, no later than 14 calendar days from the authorization.

Regarding assessment of the known and potential risks, bebtelovimab did not have any significant findings in the 3 week nonclinical toxicology studies nor any tissue binding of concern in the nonclinical GLP tissue cross-reactivity studies. In general, bebtelovimab was well tolerated in clinical trials. The overall safety database of bebtelovimab is comprised of 602 COVID-19 patients who have received an IV infusion at the authorized dose or higher. There were no serious hypersensitivity events nor anaphylaxis reported during the study of bebtelovimab. Infusion reactions that were reported within Trial PYAH were rare and considered mild or moderate. Because of the potential for more significant reactions, however, patients should be clinically monitored for at least 1 hour after infusion is complete. Bebtelovimab should 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.

The emergence of treatment emergent resistant variants is possible with the use of

bebtelovimab. The risk of resistance variants impacting clinical outcomes is not known. In order to mitigate the risk of spread of such a variant, 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.

Treatment failure is a potential risk of all monoclonal antibodies directed against the spike protein of SARS-CoV-2. Given the evolving nature of the SARS-CoV-2 variants in the United States, and because clinical samples that confirm a COVID-19 diagnosis are not typically sequenced prior to administration of these monoclonals, the clinical decision to use bebtelovimab should be made in the context of what is known about local prevalence of the circulating variants at the time of use in order to avoid possible treatment failure. Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency. At present, Omicron variant is circulating with high frequency in the United States. Given the nonclinical data demonstrating potent neutralizing activity against Omicron, use of bebtelovimab will not be restricted in any region in the United States at the time of authorization. However, FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility, and CDC regional variant frequency data[14] and will make updates to any determination to scope of use on the EUA website.[15]

Current supply of other authorized and approved products in the context of increasing Omicron infections in the U.S was a factor in the consideration of the the authorization decision for bebtelovimab. Due to the high frequency of the Omicron variant, bamlanivimab and etesevimab, as well as REGEN-COV, are not currently authorized in any U.S. region. Therefore, these drugs may not be administered for treatment under the Emergency Use Authorization until further notice by the Agency. Other recently authorized therapeutics do not have adequate supply to meet current demand of the target population. By the end of February 2022, it is expected that over (b) (4) treatment courses of bebtelovimab will be available for use.

Bebtelovimab has 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, bebtelovimab 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.

In sum, based on the the totality of the scientific information available, including the available phase 2 clinical and pharmacokinetic data, along with the nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab 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

[14] https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed February 7, 2022.
[15] https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs

viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. for the treatment of In addition, the mechanism of action for bebtelovimab is similar to other neutralizing SARS-CoV-2 monoclonal antibodies, including bamlanivimab and etesevimab, that have data from Phase 3 clinical trials showing a reduction in hospitalization or death in high risk patients infected with other SARS-CoV-2 variants. Bebtelovimab was also shown to be well tolerated in clinical trials, with a safety profile that is acceptable with monitorable risk and is comparable to other monoclonal antibodies. In addition, supply of other authorized COVID-19 treatments is limited, with current demand in excess of available approved or authorized products for use. Considered together, we believe that the known and potential benefits of treatment with bebtelovimab outweigh the known and potential risks in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

XXI. Considerations for Adverse Event (AE) Monitoring

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

The prescribing health care provider and/or the provider's designee is/are responsible for mandatory reporting of serious adverse events and all medication errors potentially related to bebtelovimab within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500. The reports should include unique identifiers and the words "bebtelovimab 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 90 cartons. Each carton will contain a leaflet with the QR code and the global URL www.bebtelovimabHCPinfo.com
  - Hard copies of the fact sheets will not be included but can be printed from the QR code or URL.
- The following URL is included on the carton of bebtelovimab: www.bebtelovimabHCPinfo.com
- Because Lilly is not supplying bebtelovimab outside of the United States at this time, www.bebtelovimabHCPinfo.com and the QR code on the leaflet will re-direct users to a US-specific site, which can also be accessed via the URL www.LillyAntibody.com/bebtelovimab.

- The URL www.LillyAntibody.com/bebtelovimab will serve as the single direct link to US-specific bebtelovimab information.

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 and Parents/Caregivers (See Section XXVI. Appendices)

XXIV. Outstanding Issues/Data Gaps

FDA has communicated that it is important to continue the clinical study of bebtelovimab. Lilly has agreed to the following condition to the Letter of Authorization:

- Lilly will submit a proposed clinical trial protocol to further evaluate bebtelovimab for the treatment of mild-to-moderate COVID-19 in non-hospitalized patients no later than March 1, 2022.

In response to FDA request, Lilly has also agreed to provide a protocol proposal within 2 weeks of authorization for a PK and safety trial to evaluate bebtelovimab in pediatric patients less than or equal to 12 years of age.

XXV. References

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

XXVI. Appendices

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR BEBTELOVIMAB

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use BEBTELOVIMAB under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for BEBTELOVIMAB.

BEBTELOVIMAB injection for intravenous use
Original EUA Authorized Date: 02/2022

----------EMERGENCY USE AUTHORIZATION----------
The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg):

- with positive results of direct SARS-CoV-2 viral testing, **and**
- who are at high risk for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. (14.4)

LIMITATIONS OF AUTHORIZED USE

- Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is l kely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency.
  - o FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant suscept bility, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. (12.4)
  - o FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
- Bebtelovimab is not authorized for use in patients who:
  - o are hospitalized due to COVID-19, OR
  - o require oxygen therapy and/or respiratory support due to COVID-19, OR
  - o require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

Bebtelovimab is not approved for any use, including for use as treatment of COVID-19. (1)

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

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------
The dosage in adults (18 years and older) and pediatric patients (≥12 years of age and weighing at least 40 kg) is bebtelovimab 175 mg administered as a single intravenous injection over at least 30 seconds. Administer bebtelovimab as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 175 mg/2 mL (87.5 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
No contraindications have been identified based on the limited available data for the emergency use of bebtelovimab authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions: Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab. If clinically significant hypersensitivity reactions occur, discontinue and initiate appropriate supportive care. Infusion-related reactions may occur up to 24 hours post injection. These reactions may be severe or life threatening. (5.1)
- Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration: Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial f brillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19. (5.2)
- Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions are infusion-related reactions (0.3%), pruritus (0.3%), and rash (0.8%). (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to bebtelovimab (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Eli Lilly and Company, Global Patient Safety: Fax: 1-317-277-0853; E-mail: mailindata_gsmtindy@lilly.com; or call 1-855-LillyC19 (1-855-545-5921) to report adverse events. (6.4).

----------DRUG INTERACTIONS----------
Bebtelovimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inh bitors of cytochrome P450 enzymes are unlikely. (7)

See FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS.

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* Sections or subsections omitted from the EUA are not listed

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab 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[16] for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate *[see Clinical Studies (14.4)]*.

LIMITATIONS OF AUTHORIZED USE

- Bebtelovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to this drug and regional variant frequency.
    - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[17]
- Bebtelovimab is not authorized for use in patients, who:
    - are hospitalized due to COVID-19, OR
    - require oxygen therapy and/or respiratory support due to COVID-19, OR
    - require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

Treatment with bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, 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)]*.

Bebtelovimab is not FDA-approved for any use, including for use as treatment of COVID-19 *[see Emergency Use Authorization (1)]*.

Bebtelovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bebtelovimab under section

[16] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

[17] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology (12.4)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic
There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use
Veklury (remdesivir) is FDA-approved for the treatment of 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, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

Although Veklury is an approved alternative treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, FDA does not consider Veklury to be an adequate alternative to bebtelovimab for this authorized use

because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration).

There are no adequate, approved and available alternatives to bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

For information on clinical studies of bebtelovimab and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The dosage in adults (18 years and older) and pediatric patients (≥12 years of age and weighing at least 40 kg) is bebtelovimab 175 mg.

Administer bebtelovimab as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset.

Bebtelovimab must be administered as a single intravenous injection over at least 30 seconds.

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, in individuals with renal impairment, or in individuals with mild hepatic impairment *[see Clinical Pharmacology (12.3)]*.

2.3 Dose Preparation and Administration

General Information

- Bebtelovimab should be prepared by a qualified healthcare professional using aseptic technique.
- Inspect bebtelovimab vial visually for particulate matter and discoloration. Bebtelovimab is clear to opalescent and colorless to slightly yellow to slightly brown solution. Discard the vial if the solution is cloudy, discolored or visible particles are observed.
- Bebtelovimab may only be administered in settings in which healthcare 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.
- **Clinically monitor patients for possible infusion-related reactions during administration and observe patients for at least 1 hour after injection is complete.**

Materials Needed for Administration

- 1 bebtelovimab vial (175 mg/2 mL)
- 1 disposable polypropylene dosing syringe capable of holding 2 mL
- 1 polycarbonate and polyvinylchloride without di-ethylhexylphthalate (DEHP) syringe extension set
- 0.9% Sodium Chloride Injection for flushing

Preparation

- Remove bebtelovimab vial 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 vial. Inspect the vial.**
- Withdraw 2 mL from the vial into the disposable syringe.
- Discard any product remaining in the vial.
- This product is preservative-free and therefore, should be administered immediately.
    - If immediate administration is not possible, store the syringe 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]). If refrigerated, allow the prepared syringe to equilibrate to room temperature for approximately 20 minutes prior to administration.
- Attach the syringe extension set.
- Prime the extension set.
- Administer the entire contents of the syringe via IV injection over at least 30 seconds.
- After the entire contents of the syringe have been administered, **flush the extension set** with 0.9% Sodium Chloride to ensure delivery of the required dose.

3 DOSAGE FORMS AND STRENGTHS

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

- Injection: 175 mg/2 mL (87.5 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

No contraindications have been identified based on the limited available data for the emergency use of bebtelovimab authorized under this EUA.

5 WARNINGS AND PRECAUTIONS

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

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of other SARS-CoV-2 monoclonal antibodies and could occur with administration of bebtelovimab. 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, which may occur up to 24 hours after the injection, have been observed in clinical trials of bebtelovimab when administered with other monoclonal

antibodies and may occur with use of bebtelovimab alone. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncope, syncope), dizziness and diaphoresis.

Administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the injection have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

5.2 Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment 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 SARS-CoV-2 monoclonal antibody 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 bebtelovimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bebtelovimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, bebtelovimab is not authorized for use in patients, regardless of age, who:

- are hospitalized due to COVID-19, OR
- require oxygen therapy and/or respiratory support due to COVID-19, OR
- require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical studies of bebtelovimab that supported the EUA. The adverse reaction rates observed in these

clinical studies cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse events associated with bebtelovimab may become apparent with more widespread use.

The safety of bebtelovimab is primarily based on exposure of 602 ambulatory (non-hospitalized) subjects who received doses of bebtelovimab, alone or in combination with bamlanivimab and etesevimab, in the phase 1 and phase 2 portions of BLAZE-4, a randomized, single-dose clinical trial.

The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher:

- Infusion-related reactions (n=2, 0.3%)
- Pruritus (n=2, 0.3%)
- Rash (n=5, 0.8%)

The most common treatment-emergent adverse events observed in subjects treated with bebtelovimab, alone or in combination with bamlanivimab and etesevimab, at the authorized dose or higher, included nausea (0.8%) and vomiting (0.7%).

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to bebtelovimab within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Bebtelovimab use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm

- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

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.

The prescribing health care provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of bebtelovimab.

*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;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

7 DRUG INTERACTIONS

Bebtelovimab is 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bebtelovimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

Data

Nonclinical reproductive toxicity studies have not been performed with bebtelovimab. In tissue cross reactivity studies using human fetal tissues, no binding of clinical concern was detected for bebtelovimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bebtelovimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bebtelovimab 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.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

8.2 Lactation

Risk Summary

There are no available data on the presence of bebtelovimab 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 bebtelovimab and any potential adverse effects on the breastfed child from bebtelovimab 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.

8.4 Pediatric Use

Bebtelovimab is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of bebtelovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of bebtelovimab as those observed in adults.

8.5 Geriatric Use

Of the 602 patients receiving bebtelovimab in BLAZE-4, 10.5% were 65 years of age and older and 3.3% were 75 years of age and older. Based on population PK analyses of samples from 573 patients over an age range of 14 to 89 years, there was no impact of age on PK. Therefore, there is no difference in the PK of bebtelovimab in geriatric patients compared to younger patients.

10 OVERDOSAGE

Doses up to 1750 mg of bebtelovimab (10 times the authorized dose of bebtelovimab) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose with bebtelovimab 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 bebtelovimab.

11 DESCRIPTION

Bebtelovimab is a human immunoglobulin G-1 (IgG1 variant) monoclonal antibody consisting of 2 identical light chain polypeptides composed of 215 amino acids each and 2 identical heavy chain polypeptides composed of 449 amino acids produced by a Chinese Hamster Ovary (CHO) stable bulk culture or cell line with a molecular weight of 144 kDa.

Bebtelovimab 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 injection.

Each mL contains 87.5 mg of bebtelovimab, 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 bebtelovimab solution has a pH range of 5.5-6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bebtelovimab is a recombinant neutralizing human IgG1κ monoclonal antibody (mAb) to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. Bebtelovimab binds the spike protein with a dissociation constant K_D = 0.046 to 0.075 nM and blocks spike protein attachment to the human ACE2 receptor with an IC_{50} value of 0.39 nM (0.056 mcg/mL).

12.2 Pharmacodynamics

The exposure-response relationships of bebtelovimab for viral loads and clinical outcomes are unknown.

12.3 Pharmacokinetics

A summary of PK parameters of bebtelovimab following administration of a single dose of 175 mg bebtelovimab is provided in Table 1.

Table 1: Pharmacokinetic Parameters of Bebtelovimab Administered IV in Adults and Pediatric Patients (12 years of age and older weighing at least 40 kg)

	Bebtelovimab (175 mg) N=573
Systemic Exposure	
Geometric Mean (%CV) C_{max}, mcg/mL	59.8 (30.1)
Geometric Mean (%CV) $C_{day\ 29}$, mcg/mL	4.35 (69.8)
Geometric Mean (%CV) AUC_{inf}, mcg day/mL	522 (39.3)
Distribution	
Geometric Mean (%CV) Vss (L)	4.61 (25.3)
Elimination	
Geometric Mean (%CV) Elimination Half-Life (day)	11.5 (25)
Geometric Mean (%CV) Clearance (L/day)	0.335 (39.3)

Abbreviations: CV = coefficient of variation; C_{max} = maximum concentration; $C_{day,29}$ = drug concentration on day 29; AUC_{inf} = area under the concentration versus time curve from zero to infinity; Vss = steady-state volume of distribution.

Specific Populations:
The PK profile of bebtelovimab was not affected by age, sex, race, or baseline viral load based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bebtelovimab in adults with COVID-19 over the body weight range of 45 kg to 194 kg.

Patients with renal impairment
Renal impairment is not expected to impact the PK of bebtelovimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of bebtelovimab.

Patients with hepatic impairment
Bebtelovimab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as other IgG monoclonal antibodies and human endogenous IgG antibodies.

Based on population PK analysis, there is no significant difference in PK of bebtelovimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bebtelovimab has not been studied in patients with moderate or severe hepatic impairment.

Drug Interactions:
Bebtelovimab is 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.

12.4 Microbiology

Antiviral Activity
The cell culture neutralization activity of bebtelovimab against SARS-CoV-2 was measured in a dose-response model quantifying plaque reduction using cultured Vero E6 cells. Bebtelovimab neutralized the USA/WA/1/2020 isolate of SARS-CoV-2 with estimated EC_{50} value = 0.044 nM (6.4 ng/mL).

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

Antibody Dependent Enhancement (ADE) of Infection
The risk that bebtelovimab 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 bebtelovimab did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of mAb down to 60,000-fold below the approximate EC_{50} value for neutralization.

Antiviral Resistance
There is a potential risk of treatment failure due to the development of viral variants that are resistant to bebtelovimab.

Nonclinical selection studies using a directed evolution of a yeast displayed Spike RBD identified that substitutions at residues K444, V445, G446, and P499 interfered with bebtelovimab's ability to block the Spike RBD:ACE-2 interaction. Pseudotyped virus-like particle (VLP) neutralization assays confirmed a 5-fold or greater reduction in susceptibility to bebtelovimab of viral variants with the following substitutions: K444N (>1,901-fold), K444Q (208-fold), K444T (>1,814-fold), V445A (111-fold), V445F (369-fold), V445G (>730-fold), G446D (69-fold), G446R (7-fold), G446V (8-fold), P499H (>1,606-fold), P499R (>1,870-fold), and P499S (25-fold). In the context of Delta spike protein, G446V substitution had reduced susceptibility of 16.4-fold.

Pseudotyped VLP assessment using the full-length spike genes from different variant lineages indicate that bebtelovimab retains activity (<5-fold reduction) against the Alpha (B.1.1.7, UK origin), Beta (B.1.351, South Africa origin), Gamma (P.1, Brazil origin), Delta (B.1.617.2, India origin), Delta [+K417N] (AY.1/AY.2, India origin), Epsilon (B.1.427/B.1.429, California origin), Iota (B.1.526, New York origin), Kappa (B.1.617.1, India origin), Lambda (C.37, Peru origin), Omicron (B.1.1.529/BA.1, South Africa origin), Omicron [+R346K] (BA.1.1), and Omicron BA.2 variant lineages (Table 2). The Mu

(B.1.621, Colombia origin) variant showed a reduction in susceptibility to bebtelovimab of 5.3-fold.

Table 2: Bebtelovimab Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Spike Protein Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[b]
B.1.351	South Africa	Beta	K417N + E484K + N501Y	No change[b]
P.1	Brazil	Gamma	K417T + E484K + N501Y	No change[b]
B.1.617.2/AY.3	India	Delta	L452R + T478K	No change[b]
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N]	L452R + T478K + K417N	No change[b]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[b]
B.1.526[c]	USA (New York)	Iota	E484K	No change[b]
B.1.617.1	India	Kappa	L452R + E484Q	No change[b]
C.37	Peru	Lambda	L452Q + F490S	No change[b]
B.1.621	Colombia	Mu	R346K + E484K + N501Y	5.3
B.1.1.529/BA.1	South Africa	Omicron	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[b]
BA.1.1	South Africa	Omicron [+R346K]	G339D + R346K + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[b]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[b]

[a] Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudotyped VLP containing the full-length spike protein reflective of the consensus sequence for each of the variant lineages were tested.
[b] No change: <5-fold reduction in susceptibility.
[c] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

In authentic SARS-CoV-2 assays, bebtelovimab retained activity (<5-fold reduction) against variant virus isolates from the Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2/AY.3), and Omicron (B.1.1.529/BA.1) lineages, as well as SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the L452R substitution present in the Epsilon (B.1.427/B.1.429) lineage or the E484K substitution present in the Iota (B.1.526) lineage (Table 3).

Table 3: Authentic[a] SARS-CoV-2 Neutralization Data for Bebtelovimab

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[b]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[c]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	No change[c]
B.1.617.2/AY.3	India	Delta	L452R, T478K	No change[c]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[c]
B.1.526[d]	USA (New York)	Iota	E484K	No change[c]
B.1.1.529/BA.1	South Africa	Omicron	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[c]

[a] The B.1.1.7, B.1.351 and B.1.617.2 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay; the B.1.1.529 variant was assessed using cell culture-expanded isolate and tested using a microneutralization assay with a CPE-based endpoint titer to determine the $IC_{>99}$, the B.1.526/E484K and B.1.427/B.1.429/L452R substitutions were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate with E484K or L452R) and tested using a plaque reduction assay.

[b] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage.

[c] No change: <5-fold reduction in susceptibility when compared to ancestral control isolate using the same methodology.

[d] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021).

Genotypic analysis and phenotypic testing are ongoing to monitor for potential bebtelovimab-resistance-associated spike variations in clinical trials. Baseline sequencing data were available for 611 of the subjects in the BLAZE-4 (Arms 9-14) Study. Of these, 551 (90.2%) were infected with a variant of interest or concern, as designated by the WHO. No subject was infected with virus of the Omicron lineage or sub-lineages. The majority of subjects in the trial were infected with Delta (49.8%) and Alpha (28.6%). These were distributed across the treatment groups with Delta and Alpha infection rates of 60.2% and 23.1% in placebo, 31.3% and 41.8% in bebtelovimab alone arms, and 58.3% and 21.9% in the bebtelovimab with bamlanivimab and etesevimab arms, respectively. Gamma and Mu infections comprised 5.6% and 3.8% of the total infections respectively. Subjects infected with Beta, Delta [+K417N], Iota, and Lambda variants were the minority with 0.5%, 0.8%, 0.7%, and 0.5% total infections, respectively. All other subjects in the trial had SARS-CoV-2 infections from either non-WHO classified viruses (2.9%), or the lineage was not able to be determined based on the baseline sequence data (6.9%). Detection of viral variants with a 5-fold or greater reduction in susceptibility to bebtelovimab at baseline have been rare, with only one G446V substitution (8-fold shift) observed transiently out of 611 subjects in the BLAZE-4 (Arms 9-14) study that had baseline sequencing available (0.2%, 1/611).

Preliminary analysis of treatment-emergent variants focused on changes at amino acid positions with known phenotypically confirmed bebtelovimab-associated variations (i.e., K444, V445, G446, and P499) in serial viral samples obtained in the BLAZE-4 (Arms 9-14) bebtelovimab Phase 2 Study. Treatment-emergent substitutions detected at ≥15% or ≥50% allele fractions at these positions included K444N, V445G, G446V, and P499H/R. These substitutions resulted in a 5-fold or greater reduction in susceptibility to bebtelovimab in pseudotyped VLP assays: K444N (>1,901-fold), V445G (>730-fold), G446V (8-fold), P499H (>1,606-fold), and P499R (>1,870-fold). Additional treatment-

emergent substitutions with no phenotypic data detected at an epitope contact position included K444E (n=1), seen in bebtelovimab-only arms, or detected at ≥15% or >50% allele fractions outside the epitope in at least 2 subjects included Q321H (n=2), C379F (n=2) and G404C (n=2), seen in bebtelovimab in combination with bamlanivimab and etesevimab arms.

Considering all substitutions detected at ≥15% allele fraction at positions K444, V445, G446, and P499, 5.0% (10/199) of subjects treated with bebtelovimab alone harbored a variant that was treatment-emergent. This was more frequent than observed in the placebo arm (0%, 0/112), or when bebtelovimab was administered together with bamlanivimab and etesevimab (0.3%, 1/312). The appearance of these treatment-emergent bebtelovimab resistance-associated substitutions was associated with higher viral loads in the subjects in whom they were detected, but none of these subjects were hospitalized. The majority of the variants were first detected on Day 5 (n=3) and Day 7 (n=6) following treatment initiation.

It is possible that bebtelovimab 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicology studies with bebtelovimab have not been conducted.

13.2 Animal Toxicology and/or Pharmacology

In toxicology studies, bebtelovimab had no adverse effects when administered intravenously to rats.

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

Antiviral Activity In Vivo
Prophylactic administration of bebtelovimab to male Syrian golden hamsters (n=5 to 8 per group) resulted in 2 to 4 $\log_{10}$ decreases in viral genomic RNA and viral replication (subgenomic RNA) from lung tissue, as well as decreases in lung weight and improvements in body weight compared to controls.

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

14 CLINICAL STUDIES

The data supporting this EUA for treatment of mild-to-moderate COVID-19 are primarily based on analyses of data from the Phase 2 portion of the BLAZE-4 trial (NCT04634409) that enrolled both low risk and high risk subjects (treatment arms 9-14). This trial evaluated the clinical efficacy data from subjects receiving 175 mg bebtelovimab alone and together with 700 mg bamlanivimab and 1,400 mg of etesevimab.

BLAZE-4 is a Phase 1/2, randomized, single-dose clinical trial evaluating treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Efficacy of bebtelovimab, alone and together with bamlanivimab and etesevimab, was evaluated in low risk adults (i.e., those not at high-risk to progress to severe COVID-19) in a randomized part of the trial which included a placebo control arm (treatment arms 9-11). Low risk adults were randomized with a 1:1:1 ratio. High-risk adults and pediatric subjects (12 years of age and older weighing at least 40 kg) received open-label active treatments. One cohort of high risk subjects was randomized with 2:1 ratio (treatment arms 12 and 13). Another cohort of high risk subject was enrolled with no randomization (treatment arm 14). The trial enrolled subjects who were not hospitalized and had 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.

BLAZE-4 was conducted prior to the emergence of the Omicron variant. No subject in BLAZE-4 was infected with virus of the Omicron lineage or sub-lineages. The majority of participants in the trial were infected with Delta (49.8%) and Alpha (28.6%).

14.1 Phase 2 Data from the Placebo-Controlled Portion of BLAZE-4 (Low Risk Subjects; Treatment Arms 9-11)

In this portion of the trial, adult subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=127), 175 mg bebtelovimab alone (N=125), or placebo (N=128). The majority (96.8%) of the subjects enrolled in these treatment arms did not meet the criteria for high-risk.

At baseline, median age was 35 years (with 1 placebo subject aged 65 or older); 56% of subjects were female, 79% were White, 36% were Hispanic or Latino, and 19% were Black or African American. Subjects had mild (74%) to moderate (26%) COVID-19; the mean duration of symptoms was 3.6 days; mean viral load by cycle threshold (CT) was 24.63 at baseline. The baseline demographics and disease characteristics were well balanced across treatment arms with the exception of baseline serology status. A higher percentage of subjects in the placebo arm were positive for baseline serology (15% vs. 9% for bamlanivimab, etesevimab, and bebtelovimab together, and 7% for bebtelovimab alone). Participants enrolled in these treatment arms had not received SARS-CoV-2 vaccine at baseline.

The primary endpoint was the proportion of subjects with persistently high viral load (PHVL) by Day 7. PHVL occurred in 26 subjects treated with placebo (21%) as compared to 16 (13%) subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together [p=0.098], and 17 (14%) subjects treated with bebtelovimab 175 mg alone [p=0.147], a 38% (95% CI: -9%, 65%) and 34% (95% CI: -15%, 62%) relative reduction, respectively.

Secondary endpoints included mean change in viral load from baseline to Day 3, 5, 7, and 11 (Figure 1).

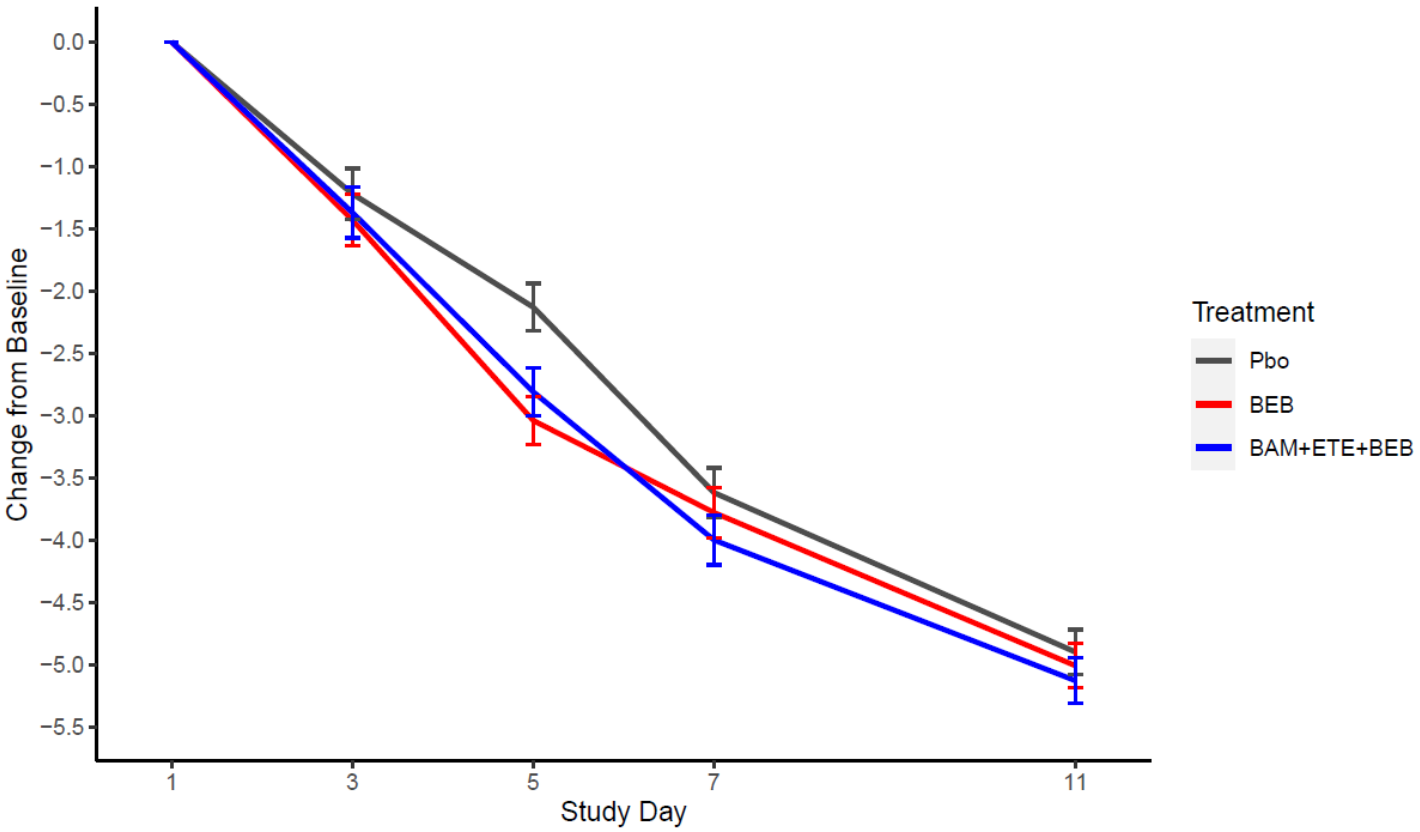

Figure 1: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Placebo-Controlled Portion of BLAZE-4 in Low Risk Adults (700 mg bamlanivimab, 1,400 mg etesevimab, 175 mg bebtelovimab together and 175 mg bebtelovimab alone).

For the secondary endpoint of COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29, these events occurred in 2 (1.6%) subjects treated with placebo as compared with 3 (2.4%) events in subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together and 2 (1.6%) events in subjects treated with bebtelovimab 175 mg alone. There was 1 subject treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together who died on Day 5. Conclusions are limited as COVID-19 related hospitalization and death rates are expected to be low in a low risk population.

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 7 days (95%CI: 6, 8 days) for subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together [p=0.289] and 6 days (95% CI: 5, 7 days) for subjects treated with bebtelovimab 175 mg alone [p=0.003] as compared with 8 days (95% CI: 7, 9 days) for subjects treated with placebo. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Sustained symptom resolution was defined as absence of any of these symptoms, except for allowance of mild fatigue and cough, in two consecutive assessments.

14.2 Phase 2 Data from the Randomized, Open-Label Portion of BLAZE-4 (High Risk Subjects; Treatment Arms 12-13)

In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=50) or 175 mg bebtelovimab alone (N=100). The majority (91.3%) of the subjects enrolled in these dose arms meet the criteria for high-risk.

At baseline, median age was 50 years (with 28 subjects aged 65 or older); 52% of subjects were female, 75% were White, 18% were Hispanic or Latino, and 18% were Black or African American. Subjects had mild (75%) to moderate (25%) COVID-19; the mean duration of symptoms was 4.7 days; mean viral load by cycle threshold (CT) was 26.66 at baseline; and 20.7% of subjects had at least one dose of a COVID-19 vaccine. There were 2 pediatric patients enrolled (ages 14 and 17), one in each treatment arm. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary objective for these treatment arms was to characterize the safety profile of bebtelovimab 175 mg by evaluating adverse events and serious adverse events. Efficacy endpoints included the proportion of subjects with COVID-19 related hospitalization or death by any cause by Day 29, mean change in viral load from baseline to Days 3, 5, 7, and 11 and time to sustained symptom resolution.

The proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause was assessed by Day 29. Events occurred in 2 (4%) subjects treated with bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg together and 3 (3%) subjects treated with bebtelovimab 175 mg alone. There was 1 subject treated with bebtelovimab 175 mg alone who died on Day 34.

Mean changes in viral load from baseline to Day 3, 5, 7, and 11 are shown in Figure 2.

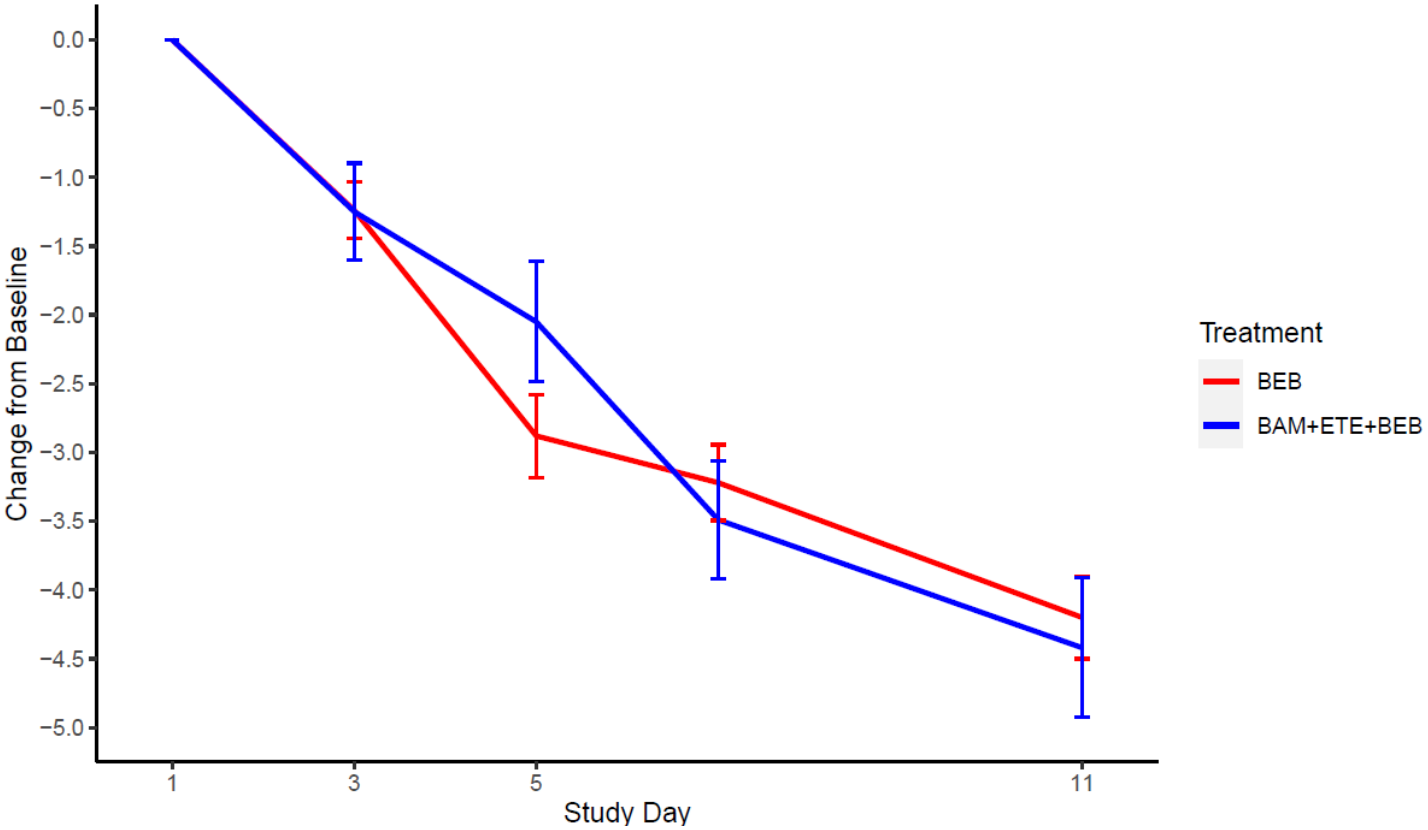

Figure 2: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Open-Label Portion of BLAZE-4 (700 mg bamlanivimab, 1,400 mg etesevimab, 175 mg bebtelovimab together and 175 mg bebtelovimab alone).

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 7 days for subjects treated with bebtelovimab 175 mg alone.

14.3 Phase 2 Data from the Non-Randomized, Open-Label Portion of BLAZE-4 (High Risk Subjects; Treatment Arm 14)

In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg (N=176). The majority (97.7%) of the subjects enrolled meet the criteria for high-risk.

At baseline, median age was 51 years (with 35 subjects aged 65 or older); 56% of subjects were female, 80% were White, 28% were Hispanic or Latino, and 16% were Black or African American. Subjects had mild (73%) to moderate (27%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 23.45 at baseline; and 31% of subjects had at least one dose of a COVID-19 vaccine. There were 2 pediatric patients enrolled (ages 14 and 15).

The primary objective for this treatment arm was to characterize the safety profile of bamlanivimab 700 mg, etesevimab 1,400 mg, and bebtelovimab 175 mg by evaluating adverse events and serious adverse events. Efficacy endpoints included the proportion of

subjects with COVID-19 related hospitalization or death by any cause by Day 29, mean change in viral load from baseline to Days 3, 5, 7, and 11, and time to sustained symptom resolution.

The proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause was assessed by Day 29. Events occurred in 3 subjects (1.7%), and no subjects died.

Mean changes in viral load from baseline to Day 3, 5, 7, and 11 were -1.4, -3.1, -4.0, and -5.4, respectively.

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 8 days.

14.4. Overall Benefit-Risk Assessment and Limitations of Data Supporting the Benefits of the Product

Based on the data from BLAZE-4, bebtelovimab has been shown to improve symptoms in patients with mild-to-moderate COVID-19. Additionally, a reduction in SARS-CoV-2 viral load on Day 5 was observed relative to placebo, though the clinical significance of this is unclear. The placebo-controlled phase 2 data are limited by enrollment of only subjects without risk factors for progression to severe COVID-19, and the trial was not powered or designed to determine a difference in the clinical outcomes of hospitalization or death between the placebo and bebtelovimab treatment arms *[see Clinical Studies (14.1)]*. Bebtelovimab has been studied in individuals who have risk factors for progression to severe COVID-19, but the efficacy analyses are limited due to the lack of a concurrent placebo control arm for this population *[see Clinical Studies (14.2, 14.3)]*.

However, based on the totality of scientific evidence available, including the available Phase 2 and pharmacokinetic data, along with the nonclinical viral neutralization data for Omicron and other variants of concern, it is reasonable to believe that bebtelovimab may be effective for the treatment of patients with mild-to-moderate COVID-19 to reduce the risk of progression to hospitalization or death. In addition, the mechanism of action for bebtelovimab is similar to other neutralizing SARS-CoV-2 monoclonal antibodies, including bamlanivimab and etesevimab, that have data from Phase 3 clinical trials showing a reduction in hospitalization or death in high risk patients infected with other SARS-CoV-2 variants. The safety profile of bebtelovimab is acceptable with monitorable risks and is comparable to other SARS-CoV-2 monoclonal antibodies, including bamlanivimab and etesevimab. Considered together, these data support that the known and potential benefits of treatment with bebtelovimab outweigh the known and potential risks in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Clinical data summarized above were similar for bebtelovimab alone as compared to the combination of bamlanivimab, etesevimab and bebtelovimab administered together. Bebtelovimab retains activity against currently circulating variants *[see Microbiology (12.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

Antibody	Concentration	Package Size	NDC
Bebtelovimab	175 mg/2 mL (87.5 mg/mL)	One vial per carton	0002-7589-01

Storage and Handling

Bebtelovimab 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.

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the “FACT SHEET FOR PATIENTS, PARENTS AND CAREGIVERS” and provide them with a copy of this Fact Sheet prior to administration of bebtelovimab. However, if providing this information will delay the administration of bebtelovimab to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after bebtelovimab administration.

Remind patients treated with bebtelovimab that they 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 additional information visit: www.LillyAntibody.com/bebtelovimab

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

18 MANUFACTURER INFORMATION

Eli Lilly and Company, Indianapolis, IN 46285, USA

Literature issued February 11, 2022

9.0-BEB-0000-EUA HCP-20220211

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

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you or your child with bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom other COVID-19 treatment options approved or authorized by FDA are not available or clinically appropriate. This Fact Sheet contains information to help you understand the potential risks and potential benefits of receiving bebtelovimab, which you or your child have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make bebtelovimab available during the COVID-19 pandemic (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). Bebtelovimab is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about bebtelovimab. Talk to your healthcare provider about your options or if you have any questions. It is your choice for you or your child to receive bebtelovimab or stop it at any time.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus (SARS-CoV-2). You 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 or your child's other medical conditions to become worse. Older people and people of all ages with severe, or long lasting (chronic) medical conditions like heart disease, lung disease, diabetes, and obesity, for example, seem to be at higher risk of being hospitalized for COVID-19. Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.

What is bebtelovimab?

Bebtelovimab is an investigational medicine used for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]):

- with positive results of direct SARS-CoV-2 viral testing, **and**

- who are at high risk[18] for progression to severe COVID-19, including hospitalization or death, **and**
- for whom other COVID-19 treatment options approved or authorized by FDA are not available or clinically appropriate.

There is limited information known about the safety and effectiveness of using bebtelovimab for the treatment of mild-to-moderate COVID-19.

For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)?**" section at the end of this Fact Sheet.

Bebtelovimab is not authorized for use in people who:
- o are likely to be infected with a SARS-CoV-2 variant that is not able to be treated by bebtelovimab based on the circulating variants in your area (ask your health care provider about FDA and CDC's latest information on circulating variants by geographic area), **or**
- o are hospitalized due to COVID-19, **or**
- o require oxygen therapy and/or respiratory support due to COVID-19, **or**
- o require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 and are on chronic oxygen therapy and/or respiratory support due to underlying non-COVID-19 related comorbidity.

What should I tell my healthcare provider before I or my child receive bebtelovimab?
Tell your healthcare provider about all your or your child's medical conditions including if you or your child:
- Have any allergies
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, and over-the-counter, vitamins, or herbal products)

How will I or my child receive bebtelovimab?
Bebtelovimab will be given as an injection through a vein (intravenously or IV) over at least 30 seconds. You will be observed by your healthcare provider for at least 1 hour after you receive bebtelovimab.

What are the important possible side effects of bebtelovimab?
- **Allergic reactions.** Allergic reactions can happen during and after injection with bebtelovimab. Tell your healthcare provider right away if you or your child develop any of the following signs and symptoms of allergic reaction: fever, difficulty breathing, low oxygen level in your blood, chills, tiredness, fast or slow heart rate,

[18] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

chest discomfort or pain, weakness, confusion, nausea, headache, shortness of breath, low or high blood pressure, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, dizziness, feeling faint, and sweating. These reactions may be severe or life threatening.

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

These are not all the possible side effects of bebtelovimab. Not many people have received bebtelovimab. Serious and unexpected side effects may happen. All of the risks are not known at this time.

It is possible that bebtelovimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, bebtelovimab may reduce the body's immune response to a vaccine for SARS-CoV-2. Talk to your healthcare provider if you have any questions.

What other treatment choices are there?
Like bebtelovimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice for you or your child to be treated or not to be treated with bebtelovimab. Should you decide not to receive it or for your child to not receive it, it will not change your or your child's standard medical care.

What if I am pregnant or breastfeeding?
There is limited experience treating pregnant women or breastfeeding mothers with bebtelovimab. For a mother and unborn baby, the benefit of receiving bebtelovimab may be greater than the risk from the treatment. If pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with bebtelovimab?

Contact your healthcare provider if you have any side effects that bother you or do not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch, or call 1-800-FDA-1088 or to Eli Lilly and Company, Inc. as shown below.

Email	Fax Number	Telephone Number
mailindata_gsmtindy@lilly.com	1-317-277-0853	1-855-LillyC19 (1-855-545-5921

How can I learn more about COVID-19?

- Ask your healthcare provider
- Visit https://www.cdc.gov/COVID19
- Contact your local or state public health department

What is an Emergency Use Authorization?

The United States FDA has made bebtelovimab available under an emergency access mechanism called an Emergency Use Authorization (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.

Bebtelovimab for the treatment of mild-to-moderate COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) **and** who are at high risk of developing severe COVID-19, including hospitalization or death, **and** for whom other COVID-19 treatment options approved or authorized by FDA are not available or clinically appropriate has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available, including data from adequate and well-controlled clinical trials, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives.

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for bebtelovimab is in effect for the duration of the COVID-19 declaration justifying emergency use of bebtelovimab, unless terminated or revoked (after which bebtelovimab may no longer be used under the EUA).

Additional Information

For general questions, visit the website or call the telephone number provided below.

Website	Telephone Number
www.LillyAntibody.com/bebtelovimab	1-855-LillyC19 (1-855-545-5921)

Literature issued February 11, 2022

Eli Lilly and Company, Indianapolis, IN 46285, USA

4.0-BEB-0000-EUA PAT-20220211

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

EUA:	111
Product:	Bebtelovimab
Sponsor:	Eli Lilly and Company
Intended Population:	Adults and pediatric patients (12 years of age and older and weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death

This addendum references the summary EUA review for bebtelovimab, dated January 7, 2022. Correct Date: February 11, 2022

Bebtelovimab is authorized for the emergency use of 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[1] for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

On pages 21 and 22 of the review, Tables 8 and 9 state the percentage of participants who were seropositive at baseline for Arms 12-13 and 14, respectively. It is of note that serostatus in this context was defined as the presence of absence of anti-SARS-CoV-2 nucleocapsid protein antibodies at baseline.

The statement of "the only TEAE reported to be severe was an occurrence of spontaneous abortion" on page 31 is incorrect. It should be amended to say that "no severe events occurred in 2 or more participants. Of gender-specific events, which have a different denominator, the only severe TEAE was an occurrence of spontaneous abortion." To clarify, this the participant received bebtelovimab with bamlanivimab and etesevimab 15 days after her last menstrual period, and not 25 days after her last menstrual period, as stated in the review.

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[1] For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

On page 34, “blister (n = 1, 0.3%)” should be included in the list of the ten nonimmediate hypersensitivity events. This event occurred in an individual who received bebtelovimab with bamlanivimab and etesevimab.

The following are corrections to CMC information on pages 46 and 47 of the review:

- Page 46, first bullet, line 5: 170mg/2ml should be changed to 175 mg/2ml. This was a typographical error.
- Page 46, third bullet, line 13: The sentence “changes in drug substance included scale up” should be deleted because all the clinical and EUA drug substance batches were manufactured at the same scale.
- Page 46, Table 23, row “Eli Lilly and Company”, lines 41-42: The term “drug product” should be deleted from the second column because Lilly did not manufacture the EUA product. The EUA drug product is manufactured at (b) (4) .
- Page 46, Table 23, row (b) (4) ”, line 46: The term “drug substance” should be deleted from the second column because (b) (4) did not manufacture the drug substance. The drug substance was manufactured at Eli Lilly and Company.
- Page 47, Table 23, row “(b) (4) ”, lines 1-2: The term “stability testing” should be deleted from the second column. (b) (4) does not perform stability testing; stability testing is conducted at (b) (4) .

These corrections replace the errors made in the January 7, 2022 summary EUA review. These corrections do not alter the conclusion of the review or alter the information presented in the authorized Facts Sheets for Healthcare Providers or for Patients, Parents and Caregivers.

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