

**Emergency Use Authorization (EUA) for bamlanivimab 700mg IV
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) ¹	90
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	Eli Lilly and Company
Submission Date(s)	October 6, 2020
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OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/Discipline(s)	Natalie Pica, MD, PhD – Clinical Reviewer Wendy Carter, DO – Cross Discipline Team Lead Michael Thomson, PhD – Clinical Virology Reviewer Jules O’Rear, PhD – Clinical Virology Team Lead Daniel Rubin, PhD – Statistics Reviewer Thamban Valappil, PhD – Statistics Team Lead Dionne Price, PhD – Director, Division of Biometrics IV Qin Sun, PhD – Clinical Pharmacology Reviewer Su-Young Choi PharmD, PhD – Clinical Pharmacology Team Lead Kellie Reynolds, PharmD – Division Director, DIDP Ye Xiong, PhD – Pharmacometrics Reviewer Justin Earp, PhD – Pharmacometrics Team Lead Yaning Wang, PhD – Division Director, DPM Deacqunita Diggs, PhD – Pharmacology/Toxicology Reviewer Christopher Ellis, PhD – Pharmacology/Toxicology Team Lead Jun Liu, PhD – Product Quality Reviewer Frances Namuswe, PhD – Product Quality Team Leader

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

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Integrated Review Completion Date	November 9, 2020
Proprietary Name	n/a
Established Name/Other names used during development	bamlanivimab (LY3819253, LY-CoV555)
Dosage Forms/Strengths	700 mg IV
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1k monoclonal antibody (mAb)
Intended Use or Need for EUA	mild to moderate COVID-19
Intended Population(s)	treatment of mild to moderate COVID-19 illness in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older, who weigh at least 40 kg, and who are at high risk for progressing to severe COVID-19 illness and/or hospitalization
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	Please refer to the Letter of Authorization for details

I. EUA Determination/Declaration

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness coronavirus disease 2019 (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 be issued for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization

B. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency
- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that bamlanivimab may be effective for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and when used under such conditions, the known and potential benefits of bamlanivimab outweigh the known and potential risks of the drug.
- There is no adequate, approved, and available alternative to the emergency use of bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

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

Proposed Use Under EUA:

Treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

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

- Have a body mass index (BMI) ≥ 35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥ 65 years of age
- Are ≥ 55 years of age AND have

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

LIMITATIONS OF AUTHORIZED USE

- Bamlanivimab is not authorized for use in patients:
 - who are hospitalized due to COVID-19, OR
 - who require oxygen therapy due to COVID-19, OR
 - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Authorized Dosage Under EUA:

Adults and Pediatric Patients:

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

Pregnant or Lactating Patients:

No dosage adjustment is recommended. Bamlanivimab has not been studied in pregnant or lactating women. Bamlanivimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

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

No dose adjustment is recommended based on age (18 to 86 years of age), sex, race, disease severity or inflammation, body weight (41 to 173 kg), renal impairment, and mild hepatic impairment. Bamlanivimab has not been studied in patients with moderate or severe hepatic impairment.

Rationale for Dose:

The dose is based on data from a randomized, double-blinded, placebo-controlled trial conducted by Eli Lilly (Trial J2W-MC-PYAB, BLAZE-1, NCT04427501). This trial enrolled patients with mild to moderate COVID-19, with or without risk factors for severe illness/hospitalization. Analysis of data from Study PYAB showed similar response across the dosage range of 700 to 7000 mg for virology, symptomology, or reduction in hospitalizations or emergency room visits. Therefore, the authorized dose of bamlanivimab is 700 mg administered as a single IV infusion over a minimum of 60 minutes. The 700mg dose achieved serum concentrations above the *in vivo* EC₉₀ value (2.3 µg/mL) for at least 28 days. Refer to sections XIII and XI for further details on the determination of the *in vivo* EC₉₀ values.

IV. Product Information (Dose Preparation and Administration)

Bamlanivimab is available as a 700 mg/20 mL (35 mg/mL) aqueous solution to be diluted prior to infusion. IND 150440 was referenced for this EUA and contains the supporting CMC information.

Preparation Instructions:

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

- Remove the bamlanivimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat.
- Inspect bamlanivimab visually for particulate matter and discoloration.
 - Bamlanivimab is a clear to slightly opalescent and colorless to slightly yellow to slightly brown solution.
- Gently invert vial by hand approximately 10 times. **Do not shake.**
- Dilute bamlanivimab using a 250 mL prefilled 0.9% Sodium Chloride Injection bag for intravenous infusion according to Table 1.
 - Withdraw and discard required volume of 0.9% Sodium Chloride Injection from infusion bag.
 - Withdraw required volume of bamlanivimab from the vial using an appropriately sized syringe.
 - Transfer bamlanivimab to the 0.9% Sodium Chloride Injection infusion bag.
 - Discard any product remaining in the vial.
- Gently invert IV bag by hand approximately 10 times to mix. **Do not shake.**
- This product is preservative-free and therefore, the prepared infusion solution should be administered immediately. If immediate administration is not possible, store the diluted bamlanivimab infusion solution for up to 24 hours at

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

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab

Treatment	Dose/Volume of Bamlanivimab (# of vials)	Volume of 0.9% sodium chloride to Discard from a 250 mL IV bag	Total Volume for Infusion	Minimum Infusion Rate	Minimum Infusion Time
Bamlanivimab	700 mg/20 mL (1 vial)	70 mL	200 mL	200 mL/hr	60 minutes

Administration:

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

- Gather the recommended materials for infusion: Polyvinylchloride (PVC) infusion set containing a 0.20/0.22 micron in-line polyethersulfone (PES) filter.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the infusion solution via pump or gravity over at least 60 minutes.
- Once infusion is complete, flush the infusion line to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Storage:

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

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

Background Information on the Condition

There are many types of human coronaviruses including some that commonly cause mild upper-respiratory tract illness. The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, approximately 46 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of November 1, 2020, including an estimated 1.2 million deaths. In the US, according to the Center for Disease Control and Prevention (CDC), as of November 3, 2020, approximately 9,268,818 cases of COVID-19 have been reported with 230,893 deaths.

Per the CDC (MMWR March 27, 2020 / 69(12);343-346), between February 12 and March 16, 2020, 4,226 COVID-19 cases were reported in the United States; 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths occurred among adults aged ≥ 65 years, with the highest percentage of severe outcomes among persons aged ≥ 85 years. These findings are similar to data from China, which indicated $>80\%$ of deaths occurred among persons aged ≥ 60 years (JAMA. 2020;323(13):1239-1242). These preliminary data also demonstrate that severe illness leading to hospitalization, including ICU admission and death, can occur in adults of any age with COVID-19. Per the CDC, adults of any age with certain underlying comorbidities or conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes, pregnancy and immunocompromised states are at increased risk for severe illness from COVID-19. Severe illness is defined as hospitalization, admission to the ICU, mechanical ventilation or death (<https://www.cdc.gov/coronavirus/2019-ncov>).

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

Therapeutic Alternatives for the Disease

There is no adequate, approved, and available alternative to the emergency use of bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

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

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

VI. Related Regulatory Submissions

As of November 7, 2020 more than 1350 participants have received an IV infusion of bamlanivimab, either alone or in combination with etesevimab, at doses ranging from 700 to 7000 mg. Etesevimab is another recombinant neutralizing human IgG1 antibody to the spike protein of SARS-CoV-2 being developed by Eli Lilly (see Table 2).

- Related INDs
 - IND 150440 – bamlanivimab as monotherapy
 - J2W-MC-PYAA: Phase 1, randomized, placebo-controlled, single ascending dose trial in hospitalized adults with moderate or severe COVID-19
 - Dose, duration, and route: single IV dose 700 mg, 2800 mg, or 7000 mg of bamlanivimab
 - Sponsor: Eli Lilly
 - J2X-MC-PYAG: Phase 1, randomized, placebo-controlled, single ascending dose trial in healthy volunteers
 - Dose, duration and route: single subcutaneous dose (b) (4) 700 mg of bamlanivimab
 - Sponsor: Eli Lilly
 - J2W-MC-PYAB: Phase 2, randomized, placebo-controlled trial in ambulatory adults with mild to moderate COVID-19 illness
 - Dose, duration and route: single IV dose 700 mg, 2800 mg, or 7000 mg of bamlanivimab
 - Sponsor: Eli Lilly
 - J2X-MC-PYAH: Phase 2, randomized, placebo-controlled trial in ambulatory adults with mild to moderate COVID-19 illness
 - Dose, duration and route: single IV dose 700 mg bamlanivimab
 - Sponsor: Eli Lilly
 - J2X-MC-PYAD: Phase 3, randomized, placebo-controlled trial in resident and staff of skilled nursing or assisted living facilities, for prophylaxis
 - Dose, duration and route: single IV dose 700 mg or 4200 mg of bamlanivimab
 - Sponsor: Eli Lilly
 - IND 150440 – bamlanivimab and etesevimab as combination therapy
 - J2W-MC-PYAB: Phase 2, randomized, placebo-controlled trial in ambulatory adults with mild to moderate COVID-19 illness, with and without at least 1 risk factor for developing severe COVID-19 illness
 - Dose, duration and route: single IV dose 2800 mg bamlanivimab + 2800 mg etesevimab

- Sponsor: Eli Lilly
- J2X-MC-PYAH: Phase 2, randomized, placebo-controlled trial in ambulatory adults with mild to moderate COVID-19 illness
 - Dose, duration and route: single IV dose (b) (4) bamlanivimab + (b) (4) etesevimab, 700 mg bamlanivimab + 1400 mg etesevimab, or 2800 mg bamlanivimab + 2800 mg etesevimab
 - Sponsor: Eli Lilly
- J2X-MC-PYAD: Phase 3, randomized, placebo-controlled trial in resident and staff of skilled nursing or assisted living facilities, for prophylaxis
 - Dose, duration and route: single IV dose (b) (4) bamlanivimab + (b) (4) etesevimab
 - Sponsor: Eli Lilly
- IND 151193
 - ACTIV-2: Phase 2/3, randomized, placebo-controlled master protocol in ambulatory patients with mild to moderate COVID-19 illness
 - Dose, duration and route: initially single IV dose 7000 mg of bamlanivimab; now protocol amended to single IV 700 mg dose of bamlanivimab
 - Sponsor: AIDS Clinical Trials Group (ACTG), National Institutes of Allergy and Infectious Disease (NIAID)
- IND 151543
 - ACTIV-3: Phase 3, randomized, placebo-controlled master protocol in patients hospitalized for COVID-19
 - Dose, duration and route: single IV dose 7000 mg of bamlanivimab
 - Sponsor: Office of Clinical Research Policy and Regulatory Operations (OCPRO), NIAID
- Related Master Files (Product Quality reviewer to provide this information)
 - DMF 21219
 - Procedure for Sterile Operations in Building B103, Indianapolis, IN
 - Sponsor: Eli Lilly

VII. Summary of Clinical Data

See Table 2 for details regarding the clinical trials.

Table 2: All Clinical Trials

Study Number	IND, NDA, or Literature Reference	Type of Study (PK, Efficacy, Safety)	Population (Planned N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
J2W-MC-PYAA	150440	PK, Efficacy, Safety	N = 24 Hospitalized patients with moderate or severe COVID-19	Phase 1, randomized, placebo-controlled, double-blind, sponsor- unblinded, single- ascending dose, first in human trial	Bamlanivimab vs placebo, single IV infusion Bamlanivimab dose cohorts: 700 mg, 2800 mg, and 7000 mg Assessments to Day 29; 60- day follow-up	Completed (DBL = 09 October 2020) Enrollment N = 26
J2W-MC-PYAB	150440	Efficacy, Safety	N = 1060 Mild to moderate COVID-19; participants in arms 7 & 8 have at least 1 risk factor for developing severe COVID-19 illness <i>Treatment Arms 1-4 & 6:</i> N = 500 participants plus additional placebo to ensure up to 50 concurrent placebo controls for treatment Arm 6 <i>Treatment Arms 7 & 8:</i> N = 250 participants per arm (Adolescents to be included as per protocol amendment dated October 20, 2020)	Phase 2, randomized, double-blind, placebo- controlled trial	Treatment vs placebo, single IV infusion Bamlanivimab dose cohorts: 700 mg, 2800 mg, or 7000 mg Combination cohort: 2800 mg bamlanivimab + 2800 mg etesevimab Assessments to Day 29; 85- day follow-up	Ongoing Enrollment N = 897
J2X-MC-PYAD	150440	Efficacy, Safety	N = ≤5000 (maximum sample size) Residents and staff of skilled nursing or assisted living facilities; Prevention and treatment cohorts Part 1 will randomize up to 1700 participants	Phase 3, randomized, double-blind, placebo- controlled study Part 1: goal of achieving ~33 events (in each of the primary and key	Bamlanivimab vs placebo, single IV infusion <u>Part 1:</u> Bamlanivimab dose: 4200 mg	Ongoing Enrollment N = 822 22 events observed

			Part 2 will randomize up to 2000 participants	secondary endpoints) in the prevention population Part 2: goal of achieving ~56 events on each of the primary and key secondary endpoints in the Prevention Cohort	<u>Part 2:</u> <u>Prevention Cohort</u> Bamlanivimab dose: 700 mg Combination dose: (b) (4) bamlanivimab + (b) (4) etesevimab Evaluation period of 8 weeks; 169-day follow-up <u>Treatment Cohort:</u> Bamlanivimab dose: 700 mg Combination dose: 2800 mg bamlanivimab + 2800 etesevimab Evaluation period of 4 weeks; 57-day follow-up	
J2X-MC-PYAG	150440	PK, Safety	N = 27 Healthy volunteers	Phase 1, randomized, placebo-controlled, participant- and investigator- blind, SC, PK trial	Bamlanivimab vs placebo, SC administration Bamlanivimab dose cohorts: (b) (4) 700 mg (b) (4) 12-week follow-up	Ongoing Enrollment N = 25
J2X-MC-PYAH	150440	Efficacy, Safety	N = 500 Mild to moderate COVID-19	Phase 2, placebo-controlled, double-blind, randomized, single-dose trial in participants with mild-to-moderate COVID-19 illness	Treatment vs placebo, single IV infusion Bamlanivimab dose: 700 mg Combination dose cohorts: (b) (4) bamlanivimab + (b) (4) etesevimab, 700 mg bamlanivimab + 1400 mg etesevimab, 2800 mg bamlanivimab + 2800 mg etesevimab	Ongoing Enrollment N = 17
ACTIV-2	151193	Efficacy, safety	N = 220 for phase 2	Phase 2/3, randomized, blinded, controlled, platform trial	Bamlanivimab vs placebo, single IV infusion	Ongoing Enrollment

			N = 1000 per arm for phase 3, inclusive of the patients enrolled in the phase 2 portion of the trial Outpatient adults positive for SARS-CoV-2		Bamlanivimab dose: 7000 mg initially, dose then changed to 700 mg 28 days of intensive follow-up, followed by limited follow-up through 24 weeks	N = 183 (N = 95 at 7000 mg dose; N = 88 at 700 mg dose) in phase 2
ACTIV-3	151543	Efficacy, Safety	N = 1000 Stage 1, N= 150 participants per IA/placebo: Inpatient adults with COVID-19 symptoms, without end organ failure Stage 2, N = 500 participants per IA/placebo (including those from Stage 1)	Phase 3, randomized, blinded, controlled platform study with 2 stages	Bamlanivimab vs placebo, IV infusion Bamlanivimab dose: 7000 mg Follow-up 90 days	Ongoing, but accrual of patients receiving bamlanivimab stopped due to lack of benefit N = 326

Source: Adapted from Applicant Submission to EUA dated November 6, 2020 entitled "Updated Table of Clinical Studies"

Abbreviations: BLA = biologics license application; COVID-19 = coronavirus disease 2019; DBL = database lock; IND = investigational new drug; IV = intravenous; N = number of participants; NDA = new drug application; PK = pharmacokinetics; SC = subcutaneous; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

VIII. Clinical Efficacy

Trial PYAB (BLAZE-1)

The main source of clinical efficacy data was from a planned interim analysis of Trial PYAB (also called BLAZE-1). This is an ongoing randomized, double-blind, placebo-controlled, phase 2 dose finding trial of bamlanivimab monotherapy and bamlanivimab + etesevimab combination therapy in outpatients with mild to moderate COVID-19. The treatment groups and sample sizes in Trial PYAB are shown in the listing below:

- Treatment arm 1: Placebo (N = 156)
- Treatment arm 2: Bamlanivimab 700 mg (N = 101)
- Treatment arm 3: Bamlanivimab 2800 mg (N = 107)
- Treatment arm 4: Bamlanivimab 7000 mg (N = 101)
- Treatment arm 5: Optional arm not entered into the study
- Treatment arm 6: Bamlanivimab 2800 mg + etesevimab 2800 mg (N = 112)
- Treatment arm 7: Bamlanivimab 2800 mg + etesevimab 2800 mg (N = 250 high risk participants planned)
- Treatment arm 8: Placebo (N = 250 high risk participants planned)

The trial began by randomizing participants to a single dose of placebo versus bamlanivimab 700 mg. The two higher bamlanivimab monotherapy doses (2800 mg and 7000 mg) were sequentially entered into the trial after being found safe in the separate phase 1 Trial PYAA. The bamlanivimab 2800 mg + etesevimab 2800 mg combination therapy was subsequently entered (treatment arm 6). Currently, results are available for treatment arms 1-4 and 6. Treatment arm 5 was an optional group that was never entered into the study. Randomization is still ongoing for treatments arms 7-8 that will allow a separately analyzed comparison of combination therapy versus placebo in approximately 500 participants at high risk for progression to more severe COVID-19 disease. This cohort is intended to provide additional evidence to support an eventual Biologics License Application.

Inclusion criteria 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. Table 3 displays demographics and baseline characteristics, which appeared relatively well balanced between treatment groups. Slightly over half of participants were female, over 40% of participants were Hispanic or Latino while under 10% were Black or African American, and on average participants had been symptomatic for slightly under 5 days before the baseline visit.

Approximately 10% of participants were seropositive for the SARS-CoV-2 virus at baseline as determined by the Elecsys Anti-SARS-CoV-2 assay.

Table 3: Baseline Demographics and Disease Characteristics in Trial PYAB

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

Source: EUA Request Table 9.2 and Regulatory Response Table APP.1 submitted October 28, 2020.

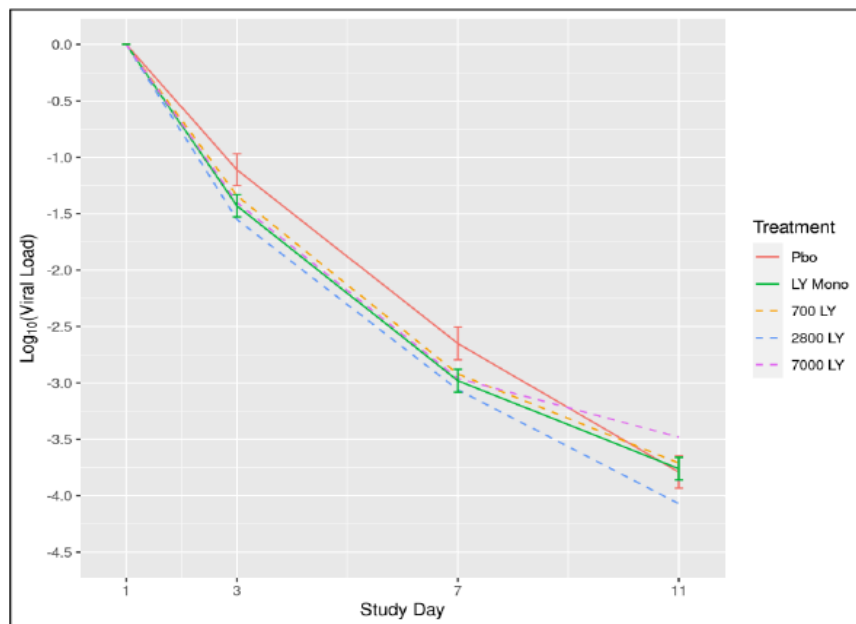
Efficacy Analyses - Virologic Endpoints

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

Results for the primary endpoint at the Day 11 visit showed significantly greater reductions from baseline viral load compared to the placebo group for the bamlanivimab 2800 mg group (p = 0.02). However, results were not significantly different from placebo for the bamlanivimab 700 mg group (p = 0.38), the bamlanivimab 7000 mg group (p = 0.70), or the group of all

combined bamlanivimab monotherapy doses ($p = 0.18$). The figure below shows mean changes in viral load over time. The figure suggests that use of an earlier timepoint than Day 11 in the mild to moderate COVID-19 population may be more sensitive for detecting treatment effects on viral load.

Figure 1: SARS-CoV-2 Viral Load Change from Baseline in Trial PYAB



Legend

Pbo = placebo (Treatment Arm 1).

LY Mono = pooled data from

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

700 LY = bamlanivimab 700 mg (Treatment Arm 2)

2800 LY = bamlanivimab 2800 mg (Treatment Arm 3).

7000 LY = bamlanivimab 7000 mg (Treatment Arm 4).

Source: EUA Request Figure 9.1.

The Applicant conducted additional analyses of virologic outcomes based on an observation from blinded data (i.e., pooled across treatment groups) that persistently high viral load at Day 7 correlated with hospitalization. Persistently high viral load was defined based on a cycle threshold value of 27.5 or less at Day 7. Table 4 shows that monotherapy was generally associated with reduced rates of persistently high viral load compared with the placebo group.

Table 4: Percentage of Participants with Persistently High SARS-CoV-2 Viral Load at Day 7 in Trial PYAB

Group	Events	Placebo – bamlanivimab difference	95% CI ^b	p-value ^c
Placebo	30/144 (21%)			
700 mg	12/99 (12%)	9%	-1% to 18%	0.09
2800 mg	9/101 (9%)	12%	3% to 21%	0.01
7000 mg	10/99 (10%)	11%	1% to 20%	0.03
Pooled Mono	31/299 (10%)	10%	3% to 18%	<0.01

^a Defined as log₁₀ viral load ≥ 5.27 (CT ≤ 27.5).

^b Confidence intervals were from the Miettinen-Nurminen method.

^c The two-sided p-values were from Fisher's exact test.

Pooled mono includes 700 mg, 2800 mg, and 7000 mg doses.

Source: EUA Request Table 9.3 and statistical reviewer.

Efficacy Analyses - Clinical Outcomes

Hospitalizations and Emergency Room (ER) visits

While viral load was used to define the primary endpoint in this phase 2 trial, the most important evidence that bamlanivimab may be effective came from the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. This endpoint is considered a clinically meaningful outcome for outpatient studies, and reliable evidence of a treatment effect on this endpoint would provide a strong basis for efficacy conclusions. Mortality was also part of this composite endpoint, but no deaths were recorded. Although there were only 14 COVID-19-related hospitalizations or emergency room visits, Table 5 shows that event rates were lower in each treatment group than in the placebo group. The pooled monotherapy group was nominally significantly superior to placebo. These superiority findings were referred to as “nominally” statistically significant because they did not correct for multiplicity due to the outcome being a secondary endpoint considered after inconclusive results for the primary endpoint, nor for multiplicity due to consideration of multiple treatment groups.

Table 5: COVID-19-Related Hospitalizations or Emergency Room Visits Within 28 Days After Treatment in Trial PYAB

Group	Events	Placebo – bamlanivimab difference	95% CI ^a	p-value ^b
Placebo	9/156 (6%)			
700 mg	1/101 (1%)	5%	0% to 10%	0.09
2800 mg	2/107 (2%)	4%	-1% to 9%	0.21
7000 mg	2/101 (2%)	4%	-2% to 9%	0.21
Pooled Mono	5/309 (2%)	4%	1% to 9%	0.02

^a Confidence intervals were from the Miettinen-Nurminen method.

^b The two-sided p-values were from Fisher's exact test.

Pooled mono includes 700 mg, 2800 mg, and 7000 mg doses.

Source: EUA Request Table 9.4 and statistical reviewer.

One potential limitation of this trial was that efficacy comparisons were not fully concurrently randomized. Specifically, the placebo group was pooled over different study periods in which the trial was randomizing to different active treatment groups. The impact of non-concurrent randomization was likely mitigated because enrollment occurred over a relatively short timeframe of less than 3 months, the randomization scheme did not lead to major imbalances between treatment groups on baseline factors, and there were no major changes observed in event rates over the study periods.

Hospitalizations and ER Visits in High Risk Subgroup

The Applicant also conducted an exploratory subgroup analysis showing that most COVID-19-related hospitalizations or emergency room visits occurred in patients classified as high risk for hospitalization. The high risk subgroup was defined according to ≥ 65 years of age, BMI ≥ 35 kg/m², chronic kidney disease, diabetes, immunosuppressive disease, or current receipt of immunosuppressive treatment. Participants were also considered high risk if they were ≥ 55 years of age and had at least one of cardiovascular disease, hypertension, or chronic obstructive pulmonary disease or another chronic respiratory disease. This analysis suggested that the difference in event rates between active treatment groups and the placebo group may be larger on the absolute scale in high risk participants. For this reason, the EUA request restricts to high risk outpatients. Likewise, the ongoing comparison of combination therapy versus placebo (treatment groups 7 and 8 in this trial) is intended to provide additional evidence of benefit in high risk outpatients.

Table 6: COVID-19-Related Hospitalizations or Emergency Room Visits in Participants Who Were at Higher Risk of Hospitalization in Trial PYAB

Group	Events	Placebo – bamlanivimab difference	95% CI ^a	p-value ^b
Placebo	7/69 (10%)			
700 mg	1/46 (2%)	8%	-2% to 18%	0.14
2800 mg	1/46 (2%)	8%	-2% to 18%	0.14
7000 mg	2/44 (5%)	6%	-6% to 16%	0.48
Pooled Mono	4/136 (3%)	7%	1% to 17%	0.05

^a Confidence intervals were from the Miettinen-Nurminen method.

^b The two-sided p-values were from Fisher's exact test.

Pooled mono includes 700 mg, 2800 mg, and 7000 mg doses.

Source: Table 4.1 of Regulatory Response submitted October 23, 2020 and statistical reviewer.

In considering the benefit-risk profile of monotherapy in the high risk population, it is useful to estimate the number needed to treat to prevent one COVID-19-related hospitalization or emergency room visit. The

estimated difference in event rates between the pooled monotherapy group and the placebo group in Table 6 corresponds to a number needed to treat of under 14 outpatients. While this would represent a major advance and would likely outweigh risks from infusion reactions, there is statistical uncertainty about this benefit as the nominal 95% confidence interval is compatible with needing to treat between 6 and 154 high risk patients to prevent one event. This uncertainty stems from the relatively small sample size and number of events.

The listing below displays characteristics of participants with COVID-19-related hospitalizations or emergency room visits. As there were only 14 participants with these clinical events, efficacy conclusions would not necessarily be robust to small changes in event counts due to missing data or adjudications. Only 2 participants required an emergency room visit without hospitalization and both were in the placebo group.

Table 7: Listing of Participants with COVID-19-Related Hospitalizations or Emergency Room Visits in Trial PYAB

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

2800 mg	79	27	M	17-Aug-20	(b) (6)	Hosp.	Weakness, shortness of breath
7000 mg	39	35	F	24-Jul-20		Hosp.	Pneumonia
7000 mg	74	31	F	27-Jul-20		Hosp	Pneumonia

Abbreviations: BMI = body mass index; ER = emergency room visit; Hosp. = hospitalization; ICU = intensive care unit; Rand. = randomization.
Source: EUA Request Table 9.6.

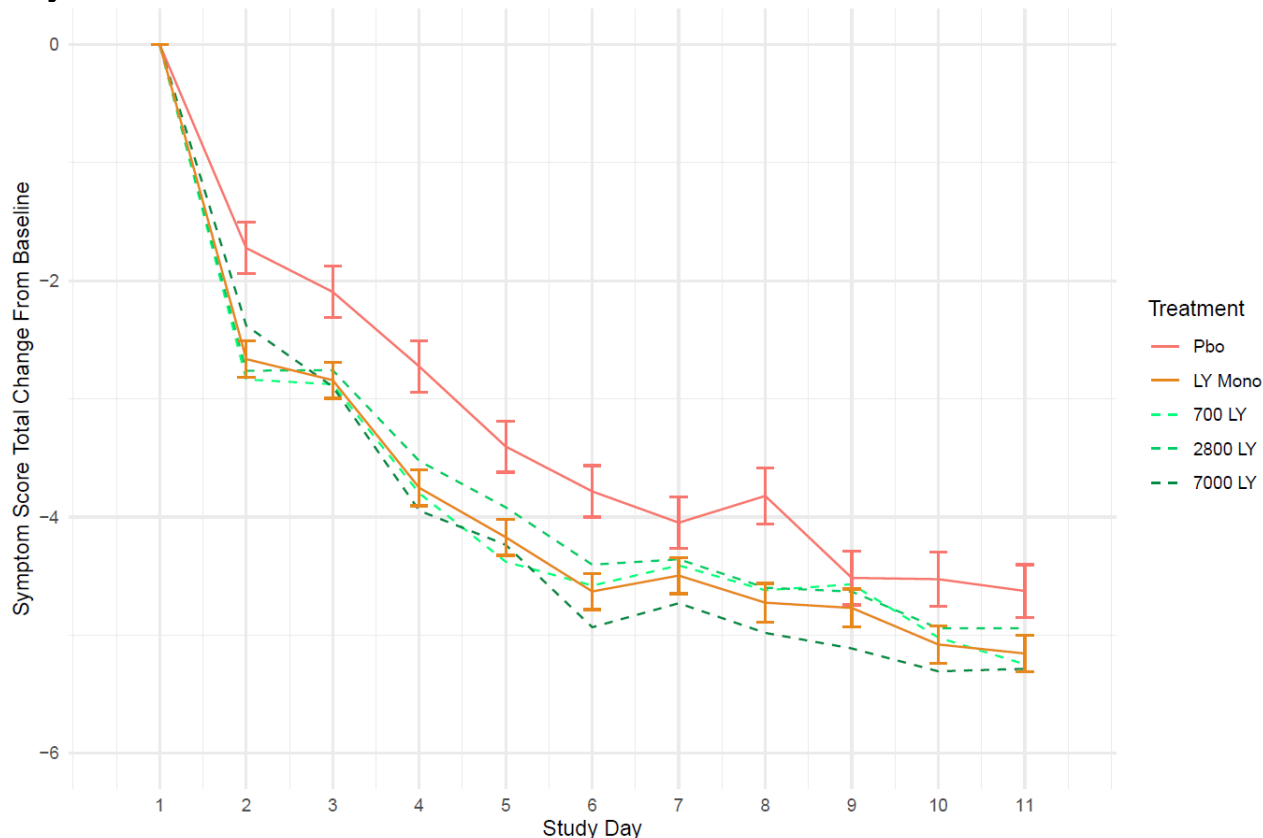
Assessment of COVID-19 Symptoms

Additional predefined secondary endpoints were based on symptom measurements, although it is currently unclear what symptom-based endpoint would be optimal for COVID-19 outpatient trials. Patients used a daily questionnaire to rate various symptoms as 0 = none or absent, 1 = mild, 2 = moderate, or 3 = severe. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Secondary endpoints included time to symptom resolution (i.e., symptoms scored as absent); symptom improvement at Days 7, 11, 15, and 22; and change from baseline in total symptom score (i.e., total rating) at Days 7, 11, 15, and 22.

Figure 2 displays mean symptom score changes from baseline. Each monotherapy dose showed statistically superior time-weighted average symptom score over Days 1-11 compared with the placebo group. However, the clinical meaningfulness of the aggregate symptom score was unclear. Differences in the time course of symptom resolution were not apparent between any of the active treatment arms.

- bamlanivimab 700 mg (p=0.009 versus placebo)
- bamlanivimab 2800 mg (p=0.038 versus placebo)
- bamlanivimab 7000 mg (p=0.011 versus placebo)

Figure 2: Mean Symptom Score Change from Baseline by Visit Through Day 11 in Trial PYAB

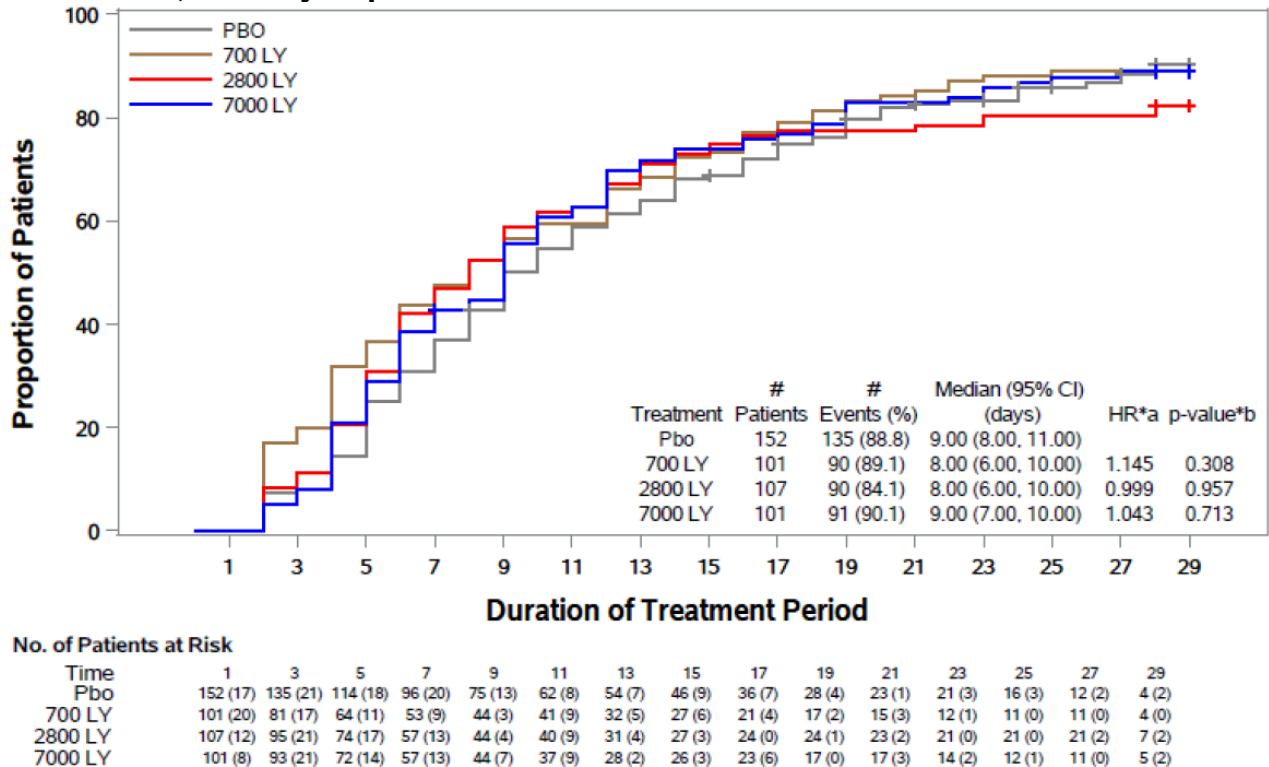


Source: EUA Request Figure 9.4 and annotated EUA factsheet Figure 2 submitted October 30, 2020.

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

Figure 3 displays results for the endpoint of time to complete resolution of all 8 COVID-19 symptoms. While the previous analysis showed that overall symptom burden was generally lower through Day 11 in active treatment groups, times to resolution appeared relatively similar between the placebo group (9 day median) and active treatment groups (8 or 9 day median for each arm). This trial was not designed to assess whether treatment could reduce rates of COVID-19 “long-haulers” with long term symptoms and disability.

Figure 3: Time to First Symptomatic Resolution, Kaplan Meier Product Limit Curve, Efficacy Population in Trial PYAB



Abbreviations: CI = confidence interval; HR = hazard ratio.

Notes: Patients at risk displayed under Day x are calculated based on patients whose time to event or censoring >Day x date. Number of events displayed under Day x are calculated based on events that occurred during the time interval from Day x (excluding Day x date) to the day of next reported Day y (including Day y date).

*a HR - stratified by duration since symptom onset to randomization.

*b Stratified log-rank for comparison with placebo.

Source: Regulatory Response Figure APP.10 received October 20, 2020.

Time from Symptom Onset

The mean duration of symptoms prior to treatment with bamlanivimab was 5 days in both treatment and placebo arms. Approximately 96% of patients were treated within 10 days of symptom onset (Table 3). At the request of DAV, additional analyses were conducted by the Applicant to determine if there were clinically significant trends or differences in outcomes based on time from symptom onset to the time of IV infusion. Evaluations of data for time from symptom onset were completed for Days 3, 5, and 7. Given that high risk individuals were a smaller subset of the overall enrolled population, there were limited data for these analyses; the samples were not powered to detect differences in the various endpoints based on time from symptom onset. There were, however, no notable differences in outcomes when considering time from symptom onset and percentage of patients with persistently high viral load at Day 7, COVID-19-related hospitalizations or ER visits, and change from baseline in SARS-CoV-2 viral load or change from baseline in total symptom score.

As such, bamlanivimab is authorized for administration as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Clinical Efficacy Conclusions

Overall, Trial PYAB provided evidence that bamlanivimab may be effective for the treatment of high risk COVID-19 outpatients. In particular, a potential benefit was seen for the secondary endpoint of COVID-19 related hospitalizations or emergency room visits, which is clinically meaningful and is considered both an individual patient and public health benefit. Results were also suggestive of reduced symptom burden with bamlanivimab through Day 11. Clinical efficacy data did not show a dose-response relationship for bamlanivimab monotherapy, which supported use of the 700 mg dose.

While the efficacy data from Trial PYAB supports that bamlanivimab may be effective for the treatment of COVID-19 in high risk outpatients, there are limitations to these findings. Limitations included multiplicity issues when considering favorable secondary endpoints and multiple dosing regimens, comparisons to the placebo group that were not fully concurrently randomized, the relatively small number of hospitalization events, and statistical uncertainty surrounding the number needed to treat to prevent serious clinical worsening.

Analysis of Spike Protein Variants and Their Impact on Virologic and Clinical Outcomes

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 an allele frequency $\geq 15\%$ were tabulated alongside viral shedding and clinical outcome data. An analysis of putative resistance-associated variants in trial PYAB focused on 3 amino acid positions in the receptor binding domain of the SARS-CoV-2 spike protein, E484, F490 and S494, which had been identified in non-clinical studies as being important for susceptibility to bamlanivimab and are predicted contact residues based on co-crystallization studies. Phenotypic data for E484K, E484Q, F490S and S494P variants showed that each had a reduction in susceptibility to bamlanivimab of >100 -fold in a SARS-CoV-2 pseudovirus neutralization assay. Each of these variants was present in the GISAID database at a frequency of $<0.02\%$ (E484K 0.015%; F490S 0.010% and S494P 0.013% of total 52,225 deposited sequences as of 11 Aug 2020).

Frequencies of baseline and treatment-emergent variants in each study arm of PYAB are shown in Table 8. Considering variants E484K, E484Q,

F490S and S494P, or all the variants occurring at these positions (other variants at these positions have not been assessed phenotypically to date), there was only one more occurrence in the 700 mg bamlanivimab group compared with placebo, and slightly higher frequencies at higher doses. For emergent variants at an allele fraction $\geq 50\%$, there were 6/98 (6.1%) in the 700 mg bamlanivimab group compared with 4/95 (4.1%) in the placebo group. Notably, in the placebo group, all instances of these variants occurred at a single time point in each subject in whom they were detected. A total of 15 emergent variants at an allele fraction $\geq 50\%$ in all bamlanivimab groups combined were detected at more than one time point, including 4/98 (4.1%) in the 700 mg bamlanivimab group. Most variants identified in Table 8 occurred disproportionately in the high-risk population (see Table 9).

Table 8: Number of Participants (%) with E484, F490 and S494 Variants

Variants	Time point	Placebo	700 mg bamlanivimab	2800 mg bamlanivimab	7000 mg bamlanivimab	Pooled bamlanivimab
Number of subjects with qualifying NGS data	Baseline	95	95	95	90	280
	Post-baseline	97	98	102	97	297
E484K/Q, F490S, S494P at $\geq 15\%$ allele fraction ^a	Baseline	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Post-baseline	6 (6.2%)	7 (7.1%)	10 (9.8%)	11 (11.3%)	28 (9.4%)
All E484, F490 and S494 variants at $\geq 15\%$ allele fraction ^b	Baseline	2 (2.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.4%)
	Post-baseline	8 (8.2%)	9 (9.2%)	12 (11.8%)	14 (14.4%)	35 (11.8%)
All variants at $\geq 50\%$ allele fraction ^c	Baseline	1 (1.1%)	0 (0%)	1 (1.1%)	0 (0%)	1 (0.4%)
	Post-baseline	4 (4.1%)	6 (6.1%)	7 (6.9%)	11 (11.3%)	24 (8.1%)
All variants at $\geq 50\%$ allele fraction detected at >1 time point ^c	Baseline	1 (1.0%)	0 (0%)	1 (1.0%)	0 (0%)	1 (0.3%)
	Post-baseline	0 (0%)	4 (4.1%)	4 (3.9%)	7 (7.2%)	15 (5.1%)

^a These variants showed loss of susceptibility to bamlanivimab in cell culture

^b Includes E484A/D/G/K/Q/V, F490L/S/V, S494L/P; only E484K/Q, F490S, S494P have been evaluated for loss of susceptibility to bamlanivimab at the time of writing.

^c Includes all variants at positions E484, F490 and S494

Source: FDA analysis of data provided in EUA-000090 [SDN 005](#)

Table 9: Number of High-Risk Participants (%) with E484, F490 and S494 Variants

Variants	Time point	Placebo	700 mg bamlanivimab	2800 mg bamlanivimab	7000 mg bamlanivimab	Pooled bamlanivimab
Number of subjects with qualifying NGS data	Baseline	38	42	40	37	119
	Post-baseline	41	43	43	44	130

E484K/Q, F490S, S494P at ≥15% allele fraction ^a	Baseline	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Post-baseline	0 (0.0%)	4 (9.3%)	9 (20.9%)	10 (22.7%)	23 (17.7%)
All E484, F490 and S494 variants at ≥15% allele fraction ^b	Baseline	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Post-baseline	1 (2.4%)	6 (14.0%)	10 (23.3%)	10 (22.7%)	26 (20.0%)
All variants at ≥50% allele fraction ^{c, d}	Baseline	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Post-baseline	0 (0.0%)	4 (9.3%)	6 (14.0%)	8 (18.2%)	18 (13.8%)
All variants at ≥50% allele fraction detected at >1 time point ^{c, d}	Baseline	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Post-baseline	0 (0.0%)	4 (9.3%)	4 (9.3%)	6 (13.6%)	14 (10.8%)
Proportion of post-baseline variants in high risk vs all subjects ^e		1/8 (12.5%)	6/9 (67%)	10/12 (83%)	10/14 (71%)	23/35 (74%)

^a These variants showed loss of susceptibility to bamlanivimab in cell culture

^b Includes E484A/D/G/K/Q/V, F490L/S/V, S494L/P; only E484K/Q, F490S, S494P have been evaluated for loss of susceptibility to bamlanivimab at the time of writing.

^c Includes all variants at positions E484, F490 and S494

^d Only E484A/K/P and S494P detected at ≥50% allele fraction

^e Includes all variants at ≥15% allele fraction at positions E484, F490 and S494

Source: FDA analysis of data provided in EUA-000090 [SDN 013](#)

The time of first appearance of the variants detected at spike protein positions E484, F490 and S494 is shown in Table 10. Variants with an allele frequency ≥50% mostly appeared at Day 7, with only a few appearing at time points later than Day 11 across study groups, which is not surprising given the lower viral shedding at Day 11 and beyond, therefore limiting the ability to detect at later time points.

Table 10: Time of First Appearance of Variant at Amino Acid Positions E484, F490, and S494

	Baseline	Day 3	Day 7	Day 11	Day 15	Day 18	Day 22	Day 25	Total
All variants ≥15% allele frequency									
Placebo	2		3	2		1	2		10
LY 700 mg		1	3	1		2	1	1	9
LY 2800 mg	1	1	6	2		1	1	1	13
LY 7000 mg		1	9	2		1	1		14
All LY	1	3	28	5	0	4	3	2	36
All variants ≥50% allele frequency									
Placebo	1		1	1			2		5
LY 700 mg		1	3	1		1			6
LY 2800 mg	1	1	4	1				1	8
LY 7000 mg		1	6	2			2		11
All LY	1	3	13	4	0	1	2	1	25

All variants $\geq 50\%$ allele frequency, high risk group									
Placebo	1								1
LY 700 mg		1	3						4
LY 2800 mg		1	4					1	6
LY 7000 mg		1	3	2			2		8
All LY	0	3	10	2	0	0	2	1	18

Source: FDA analysis of data provided in EUA-000090 [SDN 013](#)

Correlation of Putative Resistant Variant Detection with Viral Shedding

Viral shedding across the time course of study PYAB was compared for bamlanivimab-treated participants in whom a variant at positions E484, F490 and S494 was detected at $\geq 50\%$ allele fraction at any time point with those who didn't harbor such a variant (data not shown). Overall the viral shedding was higher at baseline, Days 3, 7 and 11 in subjects harboring a putative resistance variant. However, it is not clear whether the variants impacted viral RNA levels or were more likely to be selected because of higher viral shedding in these individuals. Similar virologic differences were observed for the subgroup of high-risk subjects (data not shown).

The Applicant defined virologic failure as having viral RNA levels of 5.27 \log_{10} at Day 7. The frequency was determined of participants in PYAB who had virologic failure and harbored a variant at positions E484, F490 or S494 at ≥ 1 time point (Table 11). A total of 6 (6.1%) participants in the 700 mg bamlanivimab group met the definition of virologic failure and harbored a putative resistance-associated variant, compared with 2 (2.1%) in the placebo arm. Similar frequencies were observed in higher dose groups and overall for bamlanivimab.

Table 11: Number of Participants Considered to Have Virologic Failure in Whom Putative Resistance-Associated Variants Were Detected at $\geq 15\%$ Allele Fraction ^a

Spike protein variant	Placebo (N = 97)	700 mg bamlanivimab (N = 98)	2800 mg bamlanivimab (N = 102)	7000 mg bamlanivimab (N = 97)	Pooled bamlanivimab (N = 297)
E484A	0	1	0	1	2
E484D	0	1	0	0	1
E484K	1	2	3	4	9
E484Q	0	2	3	0	5
E484V	0	0	1	0	1
F490L	1	0	0	0	0
S494P	0	1	0	0	1
# virologic failures (%)	22 (22.7%)	12 (12.2%)	9 (8.8%)	10 (10.3%)	31 (10.4%)
# virologic failures (%) with E484X, F490X or S494P	2 (2.1%)	6 (6.1%) ^b	4 (3.9%) ^c	5 (5.2%)	15 (5.1%)

- a Virologic failure defined as viral load $\geq 5.27 \log_{10}$ at Day 7. All variants included with changes at amino acid positions associated with reduced susceptibility to bamlanivimab; E484A/D/V, F490L, S494P have not been evaluated phenotypically at the time of writing
- b Includes 1 subject with E484A and S494P at different time points
- c Includes 1 subject with E484K and E484Q, 1 subject with E484K and E484Q and S494P, 1 subject with E484K and E484V
- Source: FDA analysis of data provided in EUA-000090 [SDN 013](#)

Correlation with Clinical Outcomes

Of the 15 virologic failures shown in Table 11 treated with bamlanivimab (any dose) with putative resistance-associated variants detected, 2 experienced hospitalization for COVID-19 (subject (b) (6) in 2,800 mg bamlanivimab group and subject (b) (6) in 7,000 mg bamlanivimab group). The two placebo subjects who met the definition of virologic failure and had a resistance-associated variant detected did not have a hospitalization or emergency room visit.

Table 12 shows the clinical outcomes for subjects in whom a putative resistance-associated variant was detected at ≥ 50 allele frequency at any time point, for the overall population and high-risk subjects. Overall, the Day 11 symptoms scores were similar between subjects in whom a variant was detected compared to those without a variant. Hospitalization and emergency room visits were too few overall to make firm conclusions.

Table 12: Clinical Outcomes, Stratified by All Variants $\geq 50\%$ Allele Fraction, Detected at Any Time Point

Variant	Parameter	Placebo	700 mg bamlanivimab	2800 mg bamlanivimab	7000 mg bamlanivimab	All bamlanivimab
Overall study population						
Yes	n	5	6	8	11	25
	Mean symptom score Day 11 (n)	1.4 (5)	1.7 (6)	1.9 (8)	1.8 (10)	1.8 (24)
	Hosp/ER (n)	0	0	1	1	2
No	n	94	95	95	89	279
	Mean symptom score Day 11 (n)	1.8 (83)	1.0 (87)	1.6 (81)	1.6 (82)	1.4 (250)
	Hosp/ER (n)	5	1	1	1	3
High-risk population						
Yes	n	1	4	6	8	18
	Mean symptom score Day 11 (n)	4.0 (1)	2.0 (4)	2.5 (6)	2.1 (7)	2.2 (17)
	Hosp/ER (n)	0	0	1	1	2
No	n	40	42	37	36	115
	Mean symptom score Day 11 (n)	1.9 (37)	1.1 (39)	2.2 (31)	2.5 (33)	1.9 (103)
	Hosp/ER (n)	4	1	0	1	2

Source: FDA analysis of data provided in EUA-000090 [SDN 013](#)

Summary of Resistance Data

Overall, the frequency of subjects treated with 700 mg bamlanivimab harboring a putative resistance-associated variant was similar to that of the placebo arm, although considering variants at an allele frequency of $\geq 50\%$ detected at more than 1 time point, there were 4/98 in the 700 mg bamlanivimab compared with none in the placebo group. Putative resistance-associated variants occurred disproportionately in high-risk subjects and were associated with higher viral shedding in the overall population and high-risk subjects, but it is not clear whether they caused increased viral shedding. There was a higher proportion of subjects who met virologic failure as defined by the Applicant and who harbored a putative resistance-associated variant in all bamlanivimab treatment groups compared with placebo (5.1% vs 2.1%, respectively).

The overall impact of emergent resistance-associated variants on virologic and clinical outcomes is not clear, especially given that phenotypic data are not currently available for all variants detected within and outside the epitope to which bamlanivimab binds. It is likely that there are other pathways to bamlanivimab resistance that are yet to be identified. With respect to clinical impact, there were too few hospitalizations/ER visits to determine whether resistant variant emergence contributed to negative outcomes.

IX. Clinical Safety

Bamlanivimab has been studied in patients with mild, moderate, and severe COVID-19 disease, as well as healthy participants. As of November 7, 2020, more than 1350 participants have received an IV infusion of bamlanivimab as monotherapy or in combination with etesevimab at doses ranging from 700 to 7000 mg. More than 420 participants have received a dose of 700 mg bamlanivimab or higher in Trial PYAB, which enrolled patients with mild to moderate COVID-19, with and without risk factors for severe disease and/or hospitalization. The subgroup of high-risk subjects with mild to moderate COVID-19 most closely mirror the intended patient population for use under the EUA.

Trial PYAB Safety Results

Overall Exposure for Safety Analysis in PYAB

The safety analysis of Trial PYAB is based on data from 465 subjects dosed with 700mg, 2800mg, 7000 mg of bamlanivimab or placebo. The reviewed safety data includes the interim analysis completed on 24 September 2020 as provided in the EUA request, as well as multiple

subsequent requests for additional information or analyses under the EUA application. Subjects were treated and followed for a minimum of 29 days.

Treatment-emergent adverse events (AEs) were comparable across placebo and monotherapy treatment groups. The majority of AEs were mild to moderate in severity. The incidence of mild and moderate AEs was comparable across treatment arms. While there was a higher incidence of severe AEs in the 2800 mg and 7000 mg monotherapy groups compared to placebo, these were all singular events. There were no deaths in Trial PYAB, nor any discontinuations due to AEs.

Table 13: Summary of Adverse Events in Trial PYAB

N (%)	Placebo (N = 156)	700 mg (N = 101)	2800 mg (N = 107)	7000 mg (N = 101)	Pooled Mono (N = 309)
Any AEs	41 (26%)	25 (25%)	24 (22%)	22 (22%)	71 (23%)
AEs by severity					
Mild	21 (14%)	16 (16%)	17 (16%)	10 (10%)	43 (14%)
Moderate	17 (11%)	7 (7%)	4 (4%)	7 (7%)	18 (6%)
Severe	3 (2%)	1 (1%)	3 (3%)	5 (5%)	9 (3%)
Deaths	0	0	0	0	0
SAEs	1 (1%)	0	0	0	0
DCs due to AEs	0	0	0	0	0

Abbreviations: AE = adverse event; DC = discontinuation of study drug; SAE = serious adverse event; Pooled mono includes 700 mg, 2800 mg, and 7000 mg doses

Mild=mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated; moderate=moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated; Severe=severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.

Source: EUA Request Figure 9.8

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

Table 14: Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥1% of All Patients in Trial PYAB

N (%)	Placebo (N = 156)	700 mg (N = 101)	2800 mg (N = 107)	7000 mg (N = 101)	Pooled Mono (N = 309)
Nausea	6 (4%)	3 (3%)	4 (4%)	5 (5%)	12 (4%)
Diarrhea	8 (5%)	1 (1%)	2 (2%)	7 (7%)	10 (3%)
Dizziness	3 (2%)	3 (3%)	3 (3%)	3 (3%)	9 (3%)
Headache	3 (2%)	3 (3%)	2 (2%)	0 (0%)	5 (2%)
Pruritis	1 (1%)	2 (2%)	3 (3%)	0 (0%)	5 (2%)
Vomiting	4 (3%)	1 (1%)	3 (3%)	1 (1%)	5 (2%)

Pooled mono includes 700 mg, 2800 mg, and 7000 mg doses

Source: EUA Request Table 9.9

Moderate treatment-emergent AEs were most commonly seen within the gastrointestinal disorders and nervous systems disorders system organ classes (SOC). Relative incidence of moderate adverse events was roughly equivalent across treatment groups and placebo. Most events were singular and without associated dose-dependence.

Table 15: Moderate Treatment-Emergent Adverse Events by SOC and PT Occurring in ≥1% in at Least One Treatment Group in Trial PYAB

System Organ Class Preferred Term	Placebo (N = 156)	700 mg (N = 101)	2800 mg (N = 107)	7000 mg (N = 101)	Combo (N = 112)	Pooled Mono (N = 309)	Total (N = 577)
Gastrointestinal disorders	7 (5%)	1 (1%)	1 (1%)	5 (5%)	0 (0%)	7 (2%)	14 (2%)
Nausea	4 (3%)	0 (0%)	1 (1%)	2 (2%)	0 (0%)	3 (1%)	7 (1%)
Diarrhea	2 (1%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	2 (1%)	4 (1%)
Dyspepsia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Gastroesophageal reflux disease	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Abdominal pain	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Vomiting	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)
Musculoskeletal and connective tissue disorders	2 (1%)	2 (2%)	2 (2%)	1 (1%)	0 (0%)	5 (2%)	7 (1%)
Back pain	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Musculoskeletal chest pain	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Myalgia	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Rheumatoid arthritis	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Spinal pain	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Arthralgia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Neck pain	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Nervous System Disorders	5 (3%)	2 (2%)	1 (1%)	2 (2%)	0 (0%)	5 (2%)	10 (2%)
Dizziness	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0 (0%)	3 (1%)	4 (1%)
Presyncope	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Syncope	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	2 (0%)
Dysgeusia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Headache	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0%)
Tremor	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
General Disorders and administration site conditions	0 (0%)	1 (1%)	0 (0%)	3 (3%)	1 (1%)	4 (1%)	5 (1%)
Chest discomfort	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Chills	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Fatigue	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Swelling face	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Pyrexia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Skin and subcutaneous tissue disorders	1 (1%)	0 (0%)	1 (1%)	2 (2%)	0 (0%)	3 (1%)	4 (1%)
Cold sweat	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Rash	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)

Urticaria	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	2 (0%)
Vascular disorders	0 (0%)	2 (2%)	0 (0%)	1 (1%)	1 (1%)	3 (1%)	4 (1%)
Hypertension	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	2 (1%)	2 (0%)
Deep vein thrombosis	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Orthostatic hypotension	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Investigations	0 (0%)	2 (2%)	0 (0%)	0 (0%)	1 (1%)	2 (1%)	3 (1%)
Blood pressure increased	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Hepatic enzyme increased	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)	2 (0%)
Infections and infestations	2 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	3 (1%)
Urinary tract infection	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Pelvic inflammatory disease	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Tonsillitis	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Metabolism and nutrition disorders	2 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	3 (1%)
Hypophosphatemia	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Dehydration	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0%)
Psychiatric disorders	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	2 (0%)
Insomnia	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	2 (0%)
Cardiac disorders	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Ventricular extrasystoles	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Eye disorders	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Eye pain	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Injury, poisoning and procedural complications	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Skin laceration	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	3 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)
Cough	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0%)
Nasal congestion	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Surgical and medical procedures	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Thrombectomy	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)

Source: FDA Reviewer, adapted from Regulatory Response (23Oct20_Clinical_AEs_ADAs)

The most commonly reported severe AEs were within the Respiratory, Thoracic and Mediastinal Disorders and Gastrointestinal Disorders SOC. All severe AEs were reported as singular events. Dose dependence was not appreciated.

Table 16: Severe Treatment-Emergent Adverse Events by SOC and PT Occurring in ≥1% in at Least One Treatment Group in Trial PYAB

	Placebo (N = 156)	700 mg (N = 101)	2800 mg (N = 107)	7000 mg (N = 101)	Combo (N = 112)	Pooled Mono (N = 309)	Total (N = 577)
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Musculoskeletal and connective tissue disorders	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	2 (1%)	2 (0%)
Muscle spasms	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Neck pain	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Respiratory, thoracic and mediastinal disorders	1 (1%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	2 (1%)	3 (1%)
Dyspnea	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Pulmonary embolism	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Asthma	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Gastrointestinal disorders	2 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (0%)	4 (1%)
Nausea	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (0%)	2 (0%)
Abdominal pain upper	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Hemorrhoids thrombosed	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)
Injury, poisoning and procedural complications	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Maternal exposure during pregnancy*	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Investigations	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Alanine aminotransferase increased	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Metabolism and nutrition disorders	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Hyperglycemia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Psychiatric disorders	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Insomnia	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	1 (0%)
Surgical and medical procedures	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Abortion induced*	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Nervous system disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Headache	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

*Denominator adjusted to reflect gender-specific event for females (n=85 for placebo, n=63 for 700 mg, n=51 for 2800 mg, n=58 for 7000 mg, n=58 for 2800 LY combo)

Source: FDA Reviewer, adapted from Regulatory Response (23Oct20_Clinical_AEs_ADAs)

Serious Adverse Events

Serious adverse events (SAEs) were reported in 2 participants in Trial PYAB. One SAE of upper abdominal pain was reported in a 64-year old participant who received placebo. The SAE started on Day 7 and ended on Day 10. The other SAE was reported in a 65-year old participant who received bamlanivimab 2800 mg in combination with etesevimab 2800 mg. The SAE was urinary tract infection, which started on Day 14.

Laboratory Findings

In terms of notable laboratory findings, four events of clinically significant decreases in absolute neutrophil count (ANC) were appreciated (placebo n=1, 2800 mg bamlanivimab n=2, 7000 mg bamlanivimab n=1). These decreases were not associated with other clinically significant treatment-emergent cytopenias. At the time of EUA submission, two of the four participants (2800 mg bamlanivimab n=1 and 7000 mg bamlanivimab n=1) had a return to normal values. One subject was found to have moderate hepatic enzyme increase in the 700 mg group, while another had severe alanine transaminase increase following administration of 7000 mg bamlanivimab. Severe hyperglycemia (2800 mg bamlanivimab n=1) and moderate hypophosphatemia (7000 mg bamlanivimab n=1) were also reported. Overall, there was no drug-related pattern of laboratory abnormalities.

Long-Term Follow-Up Safety

Additional information was requested to determine if there were any clinically significant safety findings in patients followed for a longer period of time. Approximately 60% of subjects in each of the three monotherapy arms and 40% of the placebo subjects had at least 60 days of post-dose follow up at the time of the database lock. In addition, 14% of subjects who received 700mg, 10% of subjects who received 2800mg, 6% of subjects who received 7000 mg and 8% of placebo subjects were followed to at least Day 85. Overall, only 7 subjects (2%) who received any dose of bamlanivimab reported at least one adverse event in the long-term follow up period. No placebo patients reported adverse events in the long-term follow up period at the time of database lock. There were no patterns of clinically significant adverse events in the long-term follow-up safety analyses.

Analysis of Submission-Specific Safety Issues

Hypersensitivity and Infusion-Related Reactions

A common reaction to intravenously-administered monoclonal antibodies is hypersensitivity, including infusion reactions. To identify potential infusion-related AEs, an analysis using broad terms within the Hypersensitivity Standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) was completed by Eli Lilly. In PYAB, the proportion of hypersensitivity reactions was similar across treatment arms and did not occur more frequently in higher dose groups (Table 17).

Table 17: Hypersensitivity Events in Trial PYAB

	Placebo (N=156)	700 mg LY (N=101)	2800 mg LY (N=107)	7000 mg LY n=101	Combo n=112
Mild	4 (3%)	3 (3%)	5 (5%)	1 (1%)	2 (2%)
Moderate	2 (1%)	2 (2%)	0 (0%)	2 (2%)	0 (0%)
Severe	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Regulatory Response (17Oct20_AEs_Symptoms_Viral Load); table generated by FDA Reviewer
Mild=mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated; moderate=moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated; Severe=severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.

Hypersensitivity events were defined as immediate if they occurred within 24 hours of administration of trial medication or placebo. There was no dose dependence across the treatment arms for immediate hypersensitivity events; albeit, only 9 events occurred overall (Table 18).

Table 18: Hypersensitivity Events by Severity in Trial PYAB that Occurred Within 24 Hours of Infusion

	Placebo n=156	700 mg LY n=101	2800 mg LY n=107	7000 mg LY n=101	Combo n=112
Mild	1 (1%)	1 (1%)	4 (4%)	0 (0%)	2 (2%)
Moderate	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Regulatory Response (17Oct20_AEs_Symptoms_Viral Load); table generated by FDA Reviewer
Mild=mild symptoms causing no or minimal interference with usual social and functional activities, with intervention not indicated; moderate=moderate symptoms causing greater than minimal interference with usual social and functional activities, with intervention indicated; Severe=severe symptoms causing inability to perform usual social and functional activities, with intervention or hospitalization indicated.

Immediate hypersensitivity events that occurred in PYAB were all mild events of flushing or pruritus, with the exception of one moderate event of facial swelling that occurred 8 hours post-dosing. All events were considered drug-related except for the event reported in the subject who received placebo (Table 19).

Table 19: Description of Hypersensitivity Events in Trial PYAB that Occurred Within 24 Hours of Infusion

Subject ID	Age/Sex/ Race	Drug/Dose	PT (verbatim)	Severity	Time Post-Dose	Investigator Considered Drug Related	Action Taken with Drug
(b) (6)	52/F/WH	700mg	Pruritus (on arm by IV site)	Mild	8 min	Yes	Drug Not Changed
	27/F/WH	700 mg	Swelling Face	Moderate	484 min	Yes	Not Applicable
	43/M/WH	2800 mg	Pruritus	Mild	28 min	Yes	Drug Interrupted
	27/M/WH	2800 mg	Pruritus	Mild	26 min	Yes	Drug Not Changed

(b) (6)	33/M/WH	2800 mg	Flushing (face)	Mild	1 min	Yes	Drug Not Changed
	40/F/WH	2800 mg	Hypersensitivity (mild allergic reaction flushing)	Mild	0 min	Yes	Not Applicable
	43/M/WH	Combo	Pruritus (left arm)	Mild	46 min	Yes	Drug Not Changed
	20/F/WH	Combo	Pruritus (Right upper arm)	Mild	70 min	Yes	Drug Not Changed
	38/F/WH	PBO	Flushing (face)	Mild	405 min	No	Drug Not Changed

Source: Regulatory Response (17Oct20_AEs_Symptoms_Viral Load); table generated by FDA Reviewer
PT= MedDRA preferred term; WH=white; F= female; M= male; PBO=placebo

Hypersensitivity events that occurred beyond the 24-hours post-dose are summarized in Table 20. In general, these events were mild to moderate, self-resolving and most were not considered related to study drug administration.

Table 20: Description of Hypersensitivity Events in Trial PYAB that Occurred Beyond 24 Hours of Infusion

Subject ID	Age/Sex/Race	Drug/Dose	PT (verbatim)	Severity	Study Day post-dose	Investigator Considered Drug Related	Action Taken
(b) (6)	23/F/WH	700 mg	Rash	Mild	14	No	Drug Not Changed
	58/F/WH	700 mg	Hypersensitivity (Allergic reaction – unknown cause)	Moderate	4	No	Not Applicable
	32/F/WH	700 mg	Pruritus	Mild	2	Yes	Drug Not Changed
	57/M/WH	2800 mg	Pruritus	Mild	10	No	Drug Not Changed
	32/F/WH	7000 mg	Urticaria	Moderate	8	No	Not Applicable
	38/M/WH	7000 mg	Stomatitis	Mild	5	No	Not Applicable
	50/F/WH	7000 mg	Rash (neck)	Moderate	5	Yes	Not Applicable
	24/F/WH	PBO	Pruritus, Swelling Face	Mild	7	No	Not Applicable
	52/F/AI	PBO	Rash	Mild	3	Not recorded	Not Applicable
	37/F/WH	PBO	Hypersensitivity (Allergic reaction –	Moderate	7	No	Not Applicable

			unknown cause)				
(b) (6)	52/F/WH	PBO	Urticaria, Asthma	Moderate, Severe	2, 13	No	Not Applicable
	53/M/WH	PBO	Conjunctivitis	Mild	3	No	Drug Not Changed

Source: Regulatory Response (17Oct20_AEs_Symptoms_Viral Load); table generated by FDA Reviewer
PT= MedDRA preferred term; WH=white; F= female; M= male; PBO=placebo

Serious Hypersensitivity Events Including Anaphylaxis in Overall Safety Database

More severe infusion-related hypersensitivity or anaphylactic events, including three SAEs have occurred during or following infusion of bamlanivimab at doses above 700 mg in other ongoing trials.

Infusion-related SAEs during infusion:

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

Infusion-related SAEs after infusion:

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

While most reported infusion reactions were mild or moderate in severity, more severe reactions are possible. In order to mitigate risks of severe infusion reactions, bamlanivimab should be administered in settings in which health care providers would have immediate access to medications to treat a severe infusion reaction such as anaphylaxis and the ability to activate the emergency medical system (EMS) as necessary. Patients should be clinically monitored during infusion and observed for at least 1 hour after infusion is complete.

Antiviral Resistance

In vitro resistance studies have identified four amino acid substitutions within the spike receptor binding domain that confer a resistant phenotype to bamlanivimab. Resistant variants were appreciated in both placebo and treatment groups in Trial PYAB. For additional information related to this potential risk, please see Section VIII, Clinical Efficacy. There is a theoretical risk that the emergence of resistant viral variants could lead to treatment failure. Additionally, it is possible that these variants could have superior fitness, leading to increased transmission in the population, with unknown implications on the initiative to develop efficacious SARS-CoV-2 vaccines.

In order to understand the potential risk of resistance to future vaccine efficacy, DAV consulted the Office of Vaccine Research and Review (OVR), Division of Viral Products (DVP) within the Center for Biologics Evaluation and Research (CBER). DVP suggested additional experiments to help determine the relative fitness and transmissibility of the resistant variants compared to wild type virus. They did note, however, that there are no other examples of monoclonal escape variants that resulted in lower vaccine efficiency at the population level, albeit few monoclonal antibodies have been used in endemic areas of infectious disease for which good vaccines are available.

Despite the proofreading mechanism of the RNA-dependent RNA polymerase of SARS-CoV-2, the spike protein D614G variant became dominant in circulating SARS-CoV-2 viruses globally in the Spring of 2020. Reassuringly, there are data indicating that vaccines encoding the wild-type spike protein will still elicit a neutralizing immune response to the D614G variant (Hou et al., bioRxiv, preprint, 29 Sept 2020 PMID: 33024969/). It is possible that the polyclonal response elicited by vaccination would still neutralize treatment-emergent variants detected following bamlanivimab administration, but more data are needed to make this determination.

While it is not known if treatment-emergent viral variants play a clinically significant role or are able to transmit efficiently, it is recommended that

patients treated with bamlanivimab 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 may reduce this theoretical risk.

Immune Response Attenuation

Administration of bamlanivimab may attenuate the endogenous immune response to SARS-CoV-2 and potentially make patients more susceptible to re-infection. Similarly, bamlanivimab administration could reduce the response to SARS-CoV-2 vaccination, though no data are available at this time to address these possible risks.

Anti-Drug Antibodies

The Applicant is currently validating anti-drug antibody (ADA) assays (screening, confirmatory, and titer assays) and will analyze stored patient samples once the assays are available. Assay validation will be completed by (b) (4). The ADA incidence and the effect of ADA after a single dose of bamlanivimab on PK, efficacy and safety are currently unknown. Monoclonal antibodies are considered to have low immunogenicity risk and the target is the spike protein of SARS-CoV-2, which is an exogenous target. In addition, for the EUA, bamlanivimab will be given as a single dose treatment.

Antibody-Dependent Enhancement of Infection

To date, there are no compelling data to support the occurrence of antibody-dependent enhancement (ADE) of infection following administration of bamlanivimab. The risk of ADE is being addressed by the Applicant in completed and ongoing non-clinical cell culture and non-human primate studies (Please see Section XIII, Nonclinical Data to Support Efficacy for more information related to ADE). The applicability of the findings from these studies to the clinical setting is not known. While there was no evidence of enhanced disease in subjects treated with bamlanivimab in Trial PYAB, or in other trials in a similar population, there is still a theoretical possibility of increased incidence of reinfection or enhanced disease if infected again once mAb concentrations have waned to sub-neutralizing concentrations in bamlanivimab-treated subjects.

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

Bamlanivimab has been studied in hospitalized patients with COVID-19 in the phase 3 master protocol trial ACTIV-3, entitled: A Multicenter,

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

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

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

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

LIMITATIONS OF AUTHORIZED USE

- Bamlanivimab is not authorized for use in patients:
 - who are hospitalized due to COVID-19, OR
 - who require oxygen therapy due to COVID-19, OR

- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

X. Specific Populations

Rationale for Inclusion of Pediatric Patients Under EUA

As of October 29, 2020, over 850,000 cases of COVID-19 have been reported in children in the United States, Puerto Rico, and Guam (<https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/>). While COVID-19 is typically milder in children, some pediatric patients require hospitalization and ICU-level care (Götzinger et al. 2020). Given that COVID-19 can be a serious and life-threatening disease in adolescent patients (particularly in those with risk factors for the development of severe illness and hospitalization), the similarities in physiology to adults, and the similar PK in adolescents weighing ≥ 40 kg based on modeling, and the safety profile, there is prospect of benefit for this patient population. Based on the totality of evidence to support the prospect of benefit and that it is reasonable to believe the known and potential benefits outweigh the known and potential risks the authorization of bamlanivimab includes adolescents who are 12 years of age and older and who weigh at least 40 kg. To date, bamlanivimab has not been administered in pediatric patients; however, clinical trials are initiating that include adolescent subjects.

Dose Considerations for Special Populations

- Safety and pharmacokinetic (PK) data are not available in children, pregnant women, lactating women, patients with renal insufficiency, or patients with moderate or severe hepatic insufficiency. No dosage adjustment is recommended based on age (18 to 86 years of age), sex, race, body weight (41 to 173 kg), renal or mild hepatic impairment, during pregnancy or while lactating, or for disease severity.
- Nonclinical reproductive toxicology studies with bamlanivimab have not been conducted.
- No binding of clinical concern with bamlanivimab to select human fetal tissues was observed in a tissue-cross reactivity study.

- No specific risks to pregnant or lactating women have been identified based on the nonclinical safety data.

XI. Clinical Pharmacology

Pharmacokinetics

- PK samples (days 1, 4, 15, 29, and 60 [available only for a few subjects]) were collected from 292 subjects enrolled in PYAA and PYAB.
- PK of bamlanivimab is linear and the exposure increased dose-proportionally following single IV doses of 700, 2800, and 7000 mg.
- The available data suggest that the PK profile of bamlanivimab is consistent with the profile of other IgG monoclonal antibodies. PK samples were analyzed currently using an LC/MS/MS method, known to be associated with low sensitivity and interference.

Rationale for Dose Based on PK/PD

- Analysis of data from Study PYAB showed similar response across the range of 700 to 7000 mg for virology, symptomology, or hospitalizations, therefore, the dose of 700 mg bamlanivimab is authorized, administered as an IV infusion over 60 minutes.
- The 700mg dose achieved serum concentrations above the *in vivo* EC₉₀ value of viral neutralization for at least 28 days in 90% of the patient population.
- Based on the virology and symptomology results, adequate drug is expected to reach lung tissues to reduce viral load at 700 mg dose.

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

- The PK of bamlanivimab was not affected by age (18 to 86 years of age), sex, race, disease severity (moderate/severe in PYAA vs. mild/moderate in PYAB) or baseline viral load based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bamlanivimab in adults with COVID-19 over the body weight range of 41 to 173 kg.
- Pediatric patients: The PK of bamlanivimab in pediatric patients have not been evaluated. Systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after accounting for the effect of body size on PK. Using modeling and simulation, the authorized dosing regimen is expected to result in comparable plasma exposures of bamlanivimab in pediatric patients aged 12 years of age or older who weigh at least 40 kg as observed in adult patients.

- Patients with renal impairment: Bamlanivimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of bamlanivimab.
- Patients with hepatic impairment: Based on population PK analysis, patients with mild hepatic impairment had approximately 20% higher clearance than patients with normal hepatic function. This effect is statistically significant, but not clinically meaningful. Bamlanivimab has not been studied in patients with moderate or severe hepatic impairment

Drug-drug Interactions

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

XIII. Nonclinical Data to Support Efficacy

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

rhesus macaque prophylaxis model; however, this model is not directly relevant to treatment indication being sought for this EUA request so is only briefly summarized below.

- Bamlanivimab bound to spike protein and receptor binding domain (RBD) with $K_D = 0.071$ nM and 2.2 nM, respectively, as determined using surface plasmon resonance (SPR). Similar experiments showed blockage of spike protein attachment to the human angiotensin converting enzyme 2 (hACE2), with an IC_{50} value of 0.025 $\mu\text{g/mL}$.
- An analysis of the crystal structure of the bamlanivimab Fab:RBD complex indicated that bamlanivimab makes close contacts (i.e., within 4.5 Å) with residues 351, 449-450, 455-456, 470, 472, 481-489, and 492-494 of the S protein.
- Bamlanivimab had an estimated mean EC_{50} value = 0.20 nM (0.03 $\mu\text{g/mL}$) and EC_{90} value = 0.61 nM (0.09 $\mu\text{g/mL}$) (EC_{90} 95% CI at 0.03, 0.3 $\mu\text{g/mL}$) against the USA/WA/1/2020 clinical isolate of SARS-CoV-2 (average of experiments run in 3 independent academic laboratories), and an estimated EC_{50} value = 0.34 nM (0.05 $\mu\text{g/mL}$) and EC_{90} value = 1.78 nM (0.26 $\mu\text{g/mL}$) against the Italy-INMI1 clinical isolate
- Serial passage of SARS-CoV-2 in cell culture in the presence of bamlanivimab identified F490S and S494P variants has having reduced susceptibility (>485-fold and >71-fold, respectively) to bamlanivimab SARS-CoV-2 neutralization. Yeast display library studies identified additional variant RBD proteins, Q493R and E484K, which had >10,000-fold and >100-fold reduced susceptibility, respectively, to bamlanivimab in a pseudovirus assay.
- Bamlanivimab demonstrated FcγR3a activity (antibody-dependent cell-mediated cytotoxicity [ADCC]) on reporter cells upon engagement by CHO cells stably co-expressing spike protein and human CD20. Bamlanivimab did not elicit complement-dependent cytotoxicity (CDC) activity in cell-based assays.
- The risk of antibody-dependent enhancement (ADE) by bamlanivimab preincubated with SARS-CoV-2 was evaluated in Thp1, Raji and ST486 (negative control) cell lines and human primary macrophages. Overall, there was no clear evidence of enhanced infection (i.e., increased intracellular or extracellular viral RNA) in any of the cell types tested. However, the Applicant may not have used sufficiently low concentrations of antibody to evaluate fully.
- An African green monkey model of SARS-CoV-2 infection was used to determine whether bamlanivimab mediated ADE *in vivo* by assessing

viral shedding in animals treated prophylactically at sub-neutralizing or neutralizing doses (0.05 mg/kg or 20 mg/kg, respectively). Comparing viral shedding/load differences in nasal and oral swabs, bronchoalveolar lavage, and lung tissue between bamlanivimab and IgG1 isotype control animals, there did not appear to be evidence of ADE. However, PK data were not provided so it is not known if sub-neutralizing concentrations of bamlanivimab were achieved in lung tissue, limiting interpretation of the data.

- In a rhesus monkey prophylaxis model (n=3 or 4 per group), using a single IV dose of bamlanivimab one day prior to challenge with SARS-CoV-2, bamlanivimab resulted in 1 to 4 log₁₀ decreases in viral load (genomic RNA) and viral replication (sub-genomic RNA) in bronchoalveolar lavage samples relative to control animals, but less of an impact on viral RNA in throat and nasal swabs following SARS-CoV-2 inoculation. The applicability of these findings to a prophylaxis or treatment setting is not known.

XIV. Supply Information

- Bamlanivimab is available in single use vials containing bamlanivimab 700 mg/20 mL per vial. Each dose requires one vial of bamlanivimab.
- The current supply includes (b) (4) vials that are packaged and labeled for immediate use. A total of (b) (4) vials will be available by the end of November 2020.
- The total supply by:
 - December 2020 is an additional (b) (4) vials (doses)
 - The total 2020 supply is (b) (4) vials (doses)
 - Q1 2021 (b) (4) vials (doses)
 - Q2 2021 is (b) (4) vials (doses)

XV. Chemistry, Manufacturing, and Controls Information

- Bamlanivimab is a recombinant neutralizing human IgG1 monoclonal antibody (molecular weight of 146 kDa) consisting of 2 identical light chain polypeptides composed of 214 amino acids each and 2 identical heavy chain polypeptides composed of 455 amino acids produced in a Chinese Hamster Ovary (CHO) cell line. Bamlanivimab was designed to target SARS-CoV-2 spike protein to block the virus attachment to hACE2 receptors, preventing subsequent viral entry into human cells and viral replication resulting in decreased viral shedding and transmission. Bamlanivimab also exhibits ADCC activity.

- Bamlanivimab Injection, 700 mg/20 mL vial, is a sterile solution formulated in an (b) (4) at pH (b) (4), consisting of (b) (4) histidine (b) (4), 50 mM sodium chloride, 6.0% sucrose, 0.05% w/v polysorbate 80, and water for injection.
- IND 150440 was referenced for this EUA and contains the supporting CMC information. The data submitted in IND 150440 support the conclusion that the manufacture of bamlanivimab is sufficiently controlled and leads to a product that is suitable for use under EUA. A non-compendial sterility test is used to release drug product (b) (4) sensitivity. For the purpose of EUA, this test is sufficient to allow for timely delivery to the patients. A full method validation to demonstrate that the non-compendial method is equivalent to or better than the compendial method is expected should the Applicant pursue licensure of bamlanivimab.
- Several major drug substance and drug product manufacturing changes were made during development of bamlanivimab, including changes in the cell line, manufacturing scales, processes, and facilities. The analytical comparability data support that the material proposed for use under the EUA is comparable to the material used in the supporting clinical studies. Differences in glycan profile, Fc receptor binding, and ADCC activity identified between the material used in the early supportive clinical studies and the EUA are not expected to change the benefit/risk analysis at the intended dose and patient population proposed for the EUA.
- The requested expiry dating of 12 months at the long-term storage condition of 2°C to 8°C for bamlanivimab drug product is supported by a risk assessment of the available drug product stability data, including 3 months at 2°C to 8°C and 3 months at accelerated storage conditions of 25°C/60% RH. Drug substance stability data for 1 month at the stress condition of 40°C further support the expiry dating. In these studies, these stability data indicate that the product remains stable and within the stability specifications with minor expected trends. The Applicant committed to update, in a timely manner, IND 150440 with additional stability data from ongoing studies to further support the proposed 12-month dating period.
- The Applicant plans to use additional manufacturing sites for bamlanivimab drug substance and drug product for this EUA. The data (e.g. comparability and manufacturing process control) supporting additional manufacturing sites will be submitted to IND 150440 prior to being used. These data will be reviewed in a timely manner to allow

rapid use of product from these sites in the EUA. Refer to section below regarding inspections.

- Data supports the assessment that the viscosity of the diluted drug product is similar to normal saline. Therefore, administration by gravity drip would be acceptable.
- Refer to OPQ EUA90 Review Memo and Product Quality IND 150440 Review Memos for detailed assessment of the Chemistry, Manufacturing, and Controls data and Information, including microbiology assessment.

XVI. Manufacturing Site Inspections

The following manufacturing and testing facilities are acceptable for the purpose of the EUA. Additional DS and DP manufacturing sites are planned to be added (refer to section above). These sites will be evaluated at the time of submission. The Applicant commitment to obtain concurrency from the Agency prior to adding additional DS and DP manufacturing and testing facilities to the EUA.

Table 21: Manufacturing Sites

Manufacturing Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant	Inspection Dates	GMP Status (if known)
ImClone Systems LLC d.b.a Eli Lilly and Company (FEI 3002889358)	Drug substance manufacturing, in-process testing	Branchburg, NJ	IND 150440	Eli Lilly and Company	08/21/2020	Official Action Indicated*

Eli Lilly and Company (FEI 1819470)	Drug product manufacturing, in-process, release, and stability testing	Indianapolis, IN	IND 150440	Eli Lilly and Company	05/25/2017	Acceptable
(b) (4)	Drug substance and drug product release/stability testing	(b) (4)	IND 150440	Eli Lilly and Company	(b) (4)	Acceptable
(b) (4)	Adventitious virus testing of (b) (4)	(b) (4)	IND 150440	Eli Lilly and Company	(b) (4)	Acceptable

* The risks associated with ImClone's manufacture of bamlanivimab drug substance under the EUA are sufficiently mitigated with specific required conditions of the authorization; Refer to OMQ memo in CMS [Case 611032 regarding Imclone](#).

With the exception of ImClone, and based on review of GMP history, no further facility-specific risks have been identified that require establishing special EUA conditions. To address the specific CGMP deviations at the Imclone site, it will be necessary for the sponsor to implement substantial risk mitigations and commitments. These extra measures will include extra controls, additional verifications, and accelerated reporting mechanisms that ensure that each bamlanivimab drug substance batch is produced following CGMP as part of this emergency authorization.

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

- No specific therapy is suggested for patients with COVID-19 who are not hospitalized in any of the following COVID-19 Treatment Guidelines:
 - The Centers for Disease Control (CDC) notes that clinical management of COVID-19 includes infection prevention and control measures as well as supportive care, which includes hospitalization for supplemental oxygen and mechanical ventilatory support when indicated. Remdesivir has been approved for the treatment of COVID-19 in certain hospitalized

patients (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html>; updated November 2, 2020).

- 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 September 25, 2020) provides 12 recommendations related to the treatment of COVID-19. IDSA does not recommend any specific therapy for the treatment of patients with mild to moderate disease who are not hospitalized.
- The NIH COVID-19 Treatment Guidelines (<https://www.covid19treatmentguidelines.nih.gov/>; updated November 3, 2020) reviews various treatments for COVID-19 and the associated available evidence. No specific antiviral or immunomodulatory therapy is recommended for patients who are not hospitalized or are hospitalized but do not require supplemental oxygen (<https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/>; updated October 9, 2020).

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Bamlanivimab is a recombinant neutralizing human IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. Bamlanivimab has demonstrated activity in cell culture and animal models against SARS-CoV-2, and is currently being evaluated in phase 1, phase 2 and phase 3 clinical trials for both prophylaxis and treatment indications.

Based on review of the topline data from the planned interim analysis of Trial J2W-MC-PYAB, also called BLAZE-1 (NCT04427501), an ongoing randomized, double-blind, placebo-controlled, phase 2 dose finding trial of bamlanivimab monotherapy in outpatients with mild to moderate COVID-19, it is reasonable to believe that bamlanivimab may be effective for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and that the known and potential benefits of bamlanivimab outweigh the known and potential risks of the drug for the proposed authorized use.

The primary endpoint for the BLAZE-1 trial was virologic, and the change from baseline of SARS-CoV-2 viral load at Day 11 was statistically significant only for 2800 mg dose, although the Day 11 time point may not have been as sensitive for detecting viral load effects as earlier time points

at which differences were more apparent. The median time to symptom improvement as recorded in a trial specific daily symptom diary was 6 days for bamlanivimab subjects, as compared with 8 days for placebo subjects. However, the clinically meaningful outcome supporting the conclusion that the drug may be effective for the proposed authorized use was the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. When considering only individuals at high risk for progression to severe disease, hospitalization or emergency room visits were reported in 10% of subjects in placebo vs 2% in the 700 mg group reported (nominal $p=0.14$) and 10% in placebo vs 3% in pooled monotherapy groups (nominal $p=0.046$).

With respect to prevention of hospitalizations among high risk patients with mild to moderate COVID-19, the estimated number needed to treat is under 14. However, there is uncertainty around this estimate of benefit due to the small numbers of events. This uncertainty is acceptable in the current setting in the U.S. with more than 100,000 new positive tests per day and hospitals at risk for exceeding bed capacity in a number of U.S. regions. Based on the BLAZE-1 placebo data, the risk of hospitalization in high risk patients is approximately 10%. Reducing this risk offers benefit to individual patients and could ameliorate a significant burden on the public health system to respond to the pandemic.

Pharmacokinetic and pharmacodynamic analyses support the 700 mg dose of bamlanivimab. Based on *in vivo* data, the 700 mg dose is expected to achieve EC₉₀ concentrations in lung tissue. The dose-response relationship was flat for the viral reduction endpoints, as well as for improvement in symptoms and in the reduction in rates of hospitalizations and emergency room visits.

Regarding assessment of the known and potential risks, the overall safety database of bamlanivimab is comprised of more than 1,350 COVID-19 patients who have received an IV infusion of bamlanivimab at doses ranging from 700 to 7000 mg, with 421 participants who received a single dose of 700 mg bamlanivimab or higher in Trial PYAB. The major adverse events of concern were hypersensitivity and infusion reactions. These were rare and were considered to be mild or moderate when patients were administered the 700 mg dose. In order to mitigate the risk of significant infusions reactions, patients should be clinically monitored for at least 1 hour after infusion is complete. Bamlanivimab should be administered in settings in which health care providers would have immediate access to medications to treat a severe infusion reaction such as anaphylaxis and the ability to activate the emergency medical system (EMS) as necessary.

While the emergence of viral variants was appreciated following treatment with bamlanivimab, the clinical relevance of this is not fully understood. Given that the relative fitness of these variants is not known, and because patients could continue to shed virus after treatment, patients should continue to self-isolate and use infection control measures (e.g. wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines in order minimize the spread of SARS-CoV-2. It is reasonable to believe that a combination of two monoclonal antibodies would be less likely to be associated with this risk of the emergence of viral variants. Going forward, the Applicant’s intention is to prioritize development of bamlanivimab in combination with a second anti-spike monoclonal antibody, etesevimab. Trials of dual therapy are ongoing.

The FDA carefully considered data available or reported from trials of hospitalized patients treated with one or more anti-spike monoclonal antibodies. Because benefit of bamlanivimab has not been observed in patients hospitalized due to COVID-19 and its use may be associated with risk of worse clinical outcomes in patients with severe COVID-19, bamlanivimab will not be authorized for patients who are hospitalized due to COVID-19, or who require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 in individuals with an underlying non-COVID-19 related comorbidity that requires chronic oxygen therapy.

The FDA reviewed information on product quality including recent manufacturing facility inspectional history. To address the specific CGMP deviations at the Imclone site, the letter of authorization will include specific conditions on quality and manufacturing that sufficiently address the risks associated with the production of bamlanivimab. These conditions include extra controls, additional verifications, and accelerated reporting mechanisms that ensure that each bamlanivimab drug substance batch is produced following CGMP as part of this emergency authorization. The conditions, among other things, also require that Lilly retain an independent third party (i.e., not affiliated with Lilly) to conduct a review of the batch records and any underlying data and associated discrepancies of bamlanivimab drug substance manufactured at Lilly Branchburg, NJ. Lilly will also retain an independent third-party (i.e., not affiliated with Lilly) to conduct laboratory release testing of bamlanivimab drug substance manufactured at Lilly Branchburg, NJ (excluding bioburden and endotoxin testing). Due to implementation timelines, independent third-party potency testing will commence on February 1, 2021. Until February 1, 2021, the Lilly Indianapolis, IN facility may conduct the equivalent of third-party potency testing.

Based on the totality of the evidence available to the FDA and considering the context of the current public health emergency in the U.S., it is reasonable to believe that bamlanivimab may be effective for the proposed authorized use and the known and potential benefits of bamlanivimab outweigh the known and potential risks of the drug. Therefore, the Review Division and the Office of Infectious Diseases conclude that the statutory standards are met and recommend authorization of an EUA for bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

XXI. Considerations for Adverse Event (AE) Monitoring

This product will either be used in clinical trials or in clinical practice. If used in clinical trials conducted under IND, FDA IND safety reporting regulations will apply. In the setting of a pandemic where practicing physicians will have many competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system.

The prescribing health care provider and/or the provider's designee will be responsible for mandatory reporting of all medication errors and all serious adverse events considered to be potentially related to bamlanivimab occurring during bamlanivimab treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Bamlanivimab Treatment under Emergency Use Authorization (EUA)."

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

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

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

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

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

- One case will include 100 cartons. Each carton contains one vial of bamlanivimab 700 mg and a leaflet with the QR code and the global URL www.bamlanivimabHCPinfo.com
 - Hard copies of the fact sheets will not be included but can be printed from the QR code or Global URL.
- The Global URL will allow users to be directed to the US URL www.bamlanivimab.com

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

- Fact Sheet for Health Care Providers (See Section XXVI. Appendices)
- Fact Sheet for Patients and Parents and Caregivers (See Section XXVI. Appendices)

XXIV. Outstanding Issues/Data Gaps

Not applicable.

XXV. References

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

XXVI. Appendices

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

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

AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product bamlanivimab for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

LIMITATIONS OF AUTHORIZED USE

- Bamlanivimab is not authorized for use in patients:
 - who are hospitalized due to COVID-19, OR
 - who require oxygen therapy due to COVID-19, OR
 - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Bamlanivimab has been authorized by FDA for the emergency uses described above. Bamlanivimab is not FDA-approved for these uses.

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

This EUA is for the use of the unapproved product bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization [see *Limitations of Authorized Use*].

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

- Have a body mass index (BMI) ≥ 35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥ 65 years of age

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

Bamlanivimab must be administered by intravenous (IV) infusion.

Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to bamlanivimab. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

- The authorized dosage for bamlanivimab is a single intravenous (IV) infusion of 700 mg administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.
- Bamlanivimab is available as concentrated solution and must be diluted prior to administration.
- Administer bamlanivimab 700 mg via IV infusion over at least 60 minutes via pump or gravity.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.
- Patients treated with bamlanivimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of bamlanivimab in COVID-19, please see www.clinicaltrials.gov.

Contraindications

None.

Dosing

Patient Selection and Treatment Initiation

This section provides essential information on the unapproved product bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization [see *Limitations of Authorized Use*].

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

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

Dosage

The dosage of bamlanivimab in adults and pediatric patients 12 years of age and older weighing at least 40 kg is a single IV infusion of 700 mg bamlanivimab administered over at least 60 minutes. Bamlanivimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

Dosage Adjustment in Specific Populations

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

Preparation and Administration

Preparation

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

- Remove the bamlanivimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat.**
- Inspect bamlanivimab visually for particulate matter and discoloration.
 - Bamlanivimab is a clear to slightly opalescent and colorless to slightly yellow to slightly brown solution.
- Gently invert vial by hand approximately 10 times. **Do not shake.**
- Dilute bamlanivimab using a 250 mL prefilled 0.9% Sodium Chloride Injection bag for intravenous infusion according to **Table 1**.
 - Withdraw and discard required volume of 0.9% Sodium Chloride Injection from infusion bag.
 - Withdraw required volume of bamlanivimab from the vial using an appropriately sized syringe.
 - Transfer bamlanivimab to the 0.9% Sodium Chloride Injection infusion bag.
 - Discard any product remaining in the vial.
- Gently invert IV bag by hand approximately 10 times to mix. **Do not shake.**
- This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted bamlanivimab infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab

Treatment	Dose/Volume of Bamlanivimab (# of vials)	Volume of 0.9% sodium chloride to Discard from a 250 mL IV bag	Total Volume for Infusion	Minimum Infusion Rate	Minimum Infusion Time
Bamlanivimab	700 mg/20 mL (1 vial)	70 mL	200 mL	200 mL/hr	60 minutes

Administration

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

- Gather the recommended materials for infusion:

- Polyvinylchloride (PVC) infusion set containing a 0.20/0.22 micron in-line polyethersulfone (PES) filter.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the infusion solution via pump or gravity over at least 60 minutes (see **Table 1**).
- Once infusion is complete, flush the infusion line to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

Storage

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

Warnings

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

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of bamlanivimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions have been observed with administration of bamlanivimab.

Signs and symptoms of infusion related reactions may include:

- fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.

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

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

Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, bamlanivimab is not authorized for use in patients [see *Limitations of Authorized Use*]:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR

- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Side Effects

Adverse events have been reported with bamlanivimab [see *Full EUA Prescribing Information, Clinical Trials Experience (6.1)*].

Additional adverse events associated with the drug may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTHCARE PROVIDERS

As the healthcare provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the “Fact Sheet for Patients, Parents and Caregivers” (and provide a copy of the Fact Sheet) prior to the patient receiving bamlanivimab, including:

- FDA has authorized the emergency use of bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization [see *Limitations of Authorized Use*].
- The patient or parent/caregiver has the option to accept or refuse bamlanivimab.
- The significant known and potential risks and benefits of bamlanivimab, and the extent to which such potential risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with bamlanivimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of bamlanivimab for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR BAMLANIVIMAB ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of bamlanivimab, the following items are required. Use of bamlanivimab under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for

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

2. As the healthcare provider, communicate to your patient or parent/caregiver, as age appropriate, information consistent with the “Fact Sheet for Patients, Parents and Caregivers” prior to the patient receiving bamlanivimab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient’s medical record that the patient/caregiver has been:
 - a. Given the “Fact Sheet for Patients, Parents and Caregivers”,
 - b. Informed of alternatives to receiving authorized bamlanivimab, and
 - c. Informed that bamlanivimab is an unapproved drug that is authorized for use under this Emergency Use Authorization.
3. Patients with known hypersensitivity to any ingredient of bamlanivimab must not receive bamlanivimab.
4. The prescribing health care provider and/or the provider’s designee are/is responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to bamlanivimab treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words “Bamlanivimab treatment under Emergency Use Authorization (EUA)” in the description section of the report.
 - Submit adverse event reports to FDA MedWatch using one of the following methods:
 - Complete and submit the report online:
www.fda.gov/medwatch/report.htm, or
 - By using a postage-paid Form FDA 3500 (available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
 - Call 1-800-FDA-1088 to request a reporting form
 - Submitted reports should include in the field name, “Describe Event, Problem, or Product Use/Medication Error” the statement “Bamlanivimab treatment under Emergency Use Authorization (EUA)”

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

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

6. **OTHER REPORTING REQUIREMENTS**

In addition, please provide a copy of all FDA MedWatch forms to:

Eli Lilly and Company, Global Patient Safety

Fax: 1-317-277-0853

E-mail: mailindata_gsmtindy@lilly.com

Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to bamlanivimab for patients who have mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization. Additional information on COVID-19 treatments can be found at <https://www.cdc.gov/coronavirus/2019-ncov/index.html>. The health care provider should visit <https://clinicaltrials.gov/> to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. FDA has issued this EUA, requested by Eli Lilly and Company for the unapproved product bamlanivimab for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.² As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that bamlanivimab may be effective for the treatment of mild to moderate COVID-19 in certain high-risk patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

² The health care provider should visit clinicaltrials.gov to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

This EUA for bamlanivimab will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

CONTACT INFORMATION

For additional information visit

www.bamlanivimab.com

If you have questions, please contact

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

END SHORT VERSION FACT SHEET
Long Version Begins on Next Page

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

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1 AUTHORIZED USE

Bamlanivimab is authorized for use under an EUA for treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

LIMITATIONS OF AUTHORIZED USE

- Bamlanivimab is not authorized for use in patients:
 - who are hospitalized due to COVID-19, OR
 - who require oxygen therapy due to COVID-19, OR
 - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, 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* (5.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

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

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

- asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

2.2 Dosage

The dosage of bamlanivimab in adults and pediatric patients 12 years of age and older weighing at least 40 kg is a single intravenous (IV) infusion of 700 mg bamlanivimab administered over at least 60 minutes. Bamlanivimab should be administered as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

2.3 Dosage Adjustment in Specific Populations

Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women [see *Use in Specific Populations* (11.1, 11.2)].

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg. Bamlanivimab is not authorized for patients weighing less than 40 kg [see *Use in Specific Populations* (11.3)].

Geriatric Use

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

Renal Impairment

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

Hepatic Impairment

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

2.4 Dose Preparation and Administration

Preparation

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

- Remove bamlanivimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat.**
- Inspect bamlanivimab visually for particulate matter and discoloration.
 - Bamlanivimab is a clear to slightly opalescent and colorless to slightly yellow to slightly brown solution.
- Gently invert vial by hand approximately 10 times. **Do not shake.**
- Dilute bamlanivimab using a 250 mL prefilled 0.9% Sodium Chloride Injection bag for intravenous infusion according to **Table 1**.
 - Withdraw and discard required volume of 0.9% Sodium Chloride Injection from the infusion bag.

- Withdraw required volume of bamlanivimab from the vial using an appropriately sized syringe.
- Transfer bamlanivimab to the 0.9% Sodium Chloride Injection infusion bag.
- Discard any product remaining in the vial.
- Gently invert IV bag by hand approximately 10 times to mix. **Do not shake.**
- This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted bamlanivimab infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab

Treatment	Dose/Volume of Bamlanivimab (# of vials)	Volume of 0.9% sodium chloride to Discard from a 250 mL IV bag	Total Volume for Infusion	Minimum Infusion Rate	Minimum Infusion Time
Bamlanivimab	700 mg/20 mL (1 vial)	70 mL	200 mL	200 mL/hr	60 minutes

Administration

Bamlanivimab solution should be administered by a qualified healthcare professional.

- Gather the recommended materials for infusion:
 - Polyvinylchloride (PVC) infusion set containing a 0.20/0.22 micron in-line polyethersulfone (PES) filter.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the infusion solution via pump or gravity over at least 60 minutes (see **Table 1**).
- Once infusion is complete, flush the infusion line to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Storage

This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted bamlanivimab solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

3 DOSAGE FORMS AND STRENGTHS

Injection: 700 mg/20 mL (35 mg/mL) as a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

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

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of bamlanivimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions have been observed with administration of bamlanivimab. Signs and symptoms of infusion related reactions may include:

- fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.

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

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

Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, bamlanivimab is not authorized for use in patients [see *Limitations of Authorized Use*]:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

6 OVERALL SAFETY SUMMARY

Over 850 subjects have been exposed to bamlanivimab in clinical trials in both hospitalized and non-hospitalized patients.

6.1 Clinical Trials Experience

The safety of bamlanivimab is based on interim data from one Phase 2 trial of 465 ambulatory (non-hospitalized) subjects with COVID-19.

BLAZE-1 is a randomized, double-blind, placebo-controlled clinical trial in ambulatory adults with mild to moderate COVID-19 symptoms who had sample collection for the first positive SARS-CoV-2 viral infection determination within 3 days prior to the start of the infusion. Subjects were treated with a single infusion of bamlanivimab at doses of 700 mg (N=101), 2,800 mg (N=107), or 7,000 mg (N=101) or placebo (N=156).

Based on data from 309 bamlanivimab-treated subjects followed for at least 28 days after treatment, adverse events occurred in 23% bamlanivimab-treated subjects and 26% of placebo-treated subjects. Serious adverse events occurred in 1 placebo-treated subject (1%) and in no bamlanivimab-treated subjects.

The most commonly reported adverse event was nausea. Table 2 shows adverse events reported in at least 1% of patients in any treatment group. Bamlanivimab is not authorized at doses of 2,800 mg or 7,000 mg.

Table 2: Treatment-emergent Adverse Events Reported in at Least 1% of All Subjects in BLAZE-1

Preferred term	Placebo N=156 %	Bamlanivimab			
		700 mg N=101 %	2,800 mg N=107 %	7,000 mg N=101 %	Total N=309 %
Nausea	4%	3%	4%	5%	4%
Diarrhea	5%	1%	2%	7%	3%
Dizziness	2%	3%	3%	3%	3%
Headache	2%	3%	2%	0%	2%
Pruritus	1%	2%	3%	0%	2%
Vomiting	3%	1%	3%	1%	2%

Hypersensitivity Including Anaphylaxis and Infusion-related Reactions:

One anaphylaxis reaction and one serious infusion-related reaction were reported during infusion of bamlanivimab in ongoing, blinded trials. The infusions were stopped. Both reactions required treatment, one required epinephrine. Both events resolved.

Immediate non-serious hypersensitivity events were noted for 2% of bamlanivimab-treated subjects and 1% of placebo-treated subjects in BLAZE-1. Reported events of pruritus, flushing and hypersensitivity were mild with one case of face swelling which was moderate. All events resolved [see *Warnings and Precautions* (5.1)].

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete [see *Warnings and Precautions* (5.1) and *Clinical Trials Experience* (6.1)].

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

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

Completion of FDA MedWatch Form to report all medication errors and serious adverse events is mandatory. The prescribing healthcare provider and/or the provider's designee are/is responsible for the mandatory reporting of all medication errors and the following selected serious adverse events occurring during bamlanivimab use and considered to be potentially related to bamlanivimab. These adverse events must be reported within 7 calendar days from the onset of the event:

- death;

- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of bamlanivimab, the prescribing healthcare provider and/or the provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Use a postage-paid Form FDA 3500 (available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA- 0178), or
- Call 1-800-FDA-1088 to request a reporting form

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding adverse events and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of bamlanivimab
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

- In section A, box 1, provide the patient's initials in the Patient Identifier
- In section A, box 2, provide the patient's date of birth
- In section B, box 5, description of the event:
 - Write "Bamlanivimab treatment under Emergency Use Authorization (EUA)" as the first line
 - Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
- In section G, box 1, name and address:
 - Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
 - Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

In addition, please provide a copy of all FDA MedWatch forms to:

Eli Lilly and Company, Global Patient Safety

Fax: 1-317-277-0853

E-mail: mailindata_gsmtindy@lilly.com

Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

10 DRUG INTERACTIONS

Bamlanivimab 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.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bamlanivimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

11.2 Lactation

Risk Summary

There are no available data on the presence of bamlanivimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bamlanivimab and any potential adverse effects on the breastfed child from bamlanivimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

The safety and effectiveness of bamlanivimab have not been assessed in pediatric patients. The recommended dosing regimen is expected to result in comparable serum exposures of

bamlanivimab in patients 12 years of age and older and weighing at least 40 kg as observed in adults, based on a pharmacokinetic (PK) modeling approach which accounted for effect of body weight changes associated with age on clearance and volume of distribution.

11.4 Geriatric Use

Of the 309 patients receiving bamlanivimab in BLAZE-1, 11% were 65 years of age and older and 3% were 75 years of age and older. Based on population PK analyses, there is no difference in PK in geriatric patients compared to younger patients.

11.5 Renal Impairment

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

11.6 Hepatic Impairment

Based on population PK analysis, patients with mild hepatic impairment had approximately 20% higher clearance than patients with normal hepatic function. This effect is statistically significant, but not clinically meaningful. Bamlanivimab has not been studied in patients with moderate or severe hepatic impairment.

11.7 Other Specific Populations

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

12 OVERDOSAGE

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

13 DESCRIPTION

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

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

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

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

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

14.2 Pharmacodynamics

A Phase 2 trial evaluated bamlanivimab over a dose range of 1 to 10 times the recommended dose (700 to 7000 mg) of bamlanivimab in patients with mild to moderate COVID-19. A flat exposure-response relationship for efficacy was identified for bamlanivimab within this dose range, based on viral load and clinical outcomes.

14.3 Pharmacokinetics

Pharmacokinetic profile of bamlanivimab is expected to be consistent with the profile of other IgG1 monoclonal antibodies.

Special Populations:

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

Pediatric population

The PK of bamlanivimab in pediatric patients have not been evaluated.

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

Patients with renal impairment

Bamlanivimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of bamlanivimab [see *Use in Specific Populations* (11.5)].

Patients with hepatic impairment

Based on population PK analysis, patients with mild hepatic impairment had approximately 20% higher clearance than patients with normal hepatic function. This effect is statistically significant, but not clinically meaningful. Bamlanivimab has not been studied in patients with moderate or severe hepatic impairment [see *Use in Specific Populations* (11.6)].

Drug interactions:

Bamlanivimab 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 [see *Drug Interactions* (10)].

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

The cell culture neutralization activity of bamlanivimab against SARS-CoV-2 was measured in a dose-response model using cultured Vero E6 cells. Bamlanivimab neutralized SARS-CoV-2 with an estimated EC₅₀ value = 0.03 µg/mL and an estimated EC₉₀ value = 0.09 µg/mL.

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

Antibody Dependent Enhancement (ADE) of Infection

The risk that bamlanivimab could mediate viral uptake and replication by immune cells was studied in THP-1 and Raji cell lines and primary human macrophages. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS CoV-2 at concentrations of bamlanivimab down to 100-fold below the EC₅₀ value.

Antiviral Resistance

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

Non-clinical studies using serial passage of SARS-CoV-2 and directed evolution of the spike protein identified E484K, F490S, Q493R and S494P, amino acid substitutions in the spike protein receptor binding domain, that had reduced susceptibility to bamlanivimab as determined in neutralization assays using SARS-CoV-2 (F490S and S494P: >485-fold and >71-fold reduction, respectively) and/or vesicular stomatitis virus-based pseudovirus (all variants >100-fold reduction).

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab-resistance-associated spike variations in clinical trials. Known bamlanivimab-resistant variants at baseline were observed at a frequency of 0.27% (1/375) in Part A of clinical trial BLAZE-1. In the same trial, treatment-emergent variants were detected at spike protein amino acid positions E484, F490 and S494, and included E484A/D/G/K/Q/V, F490L/S/V and S494L/P; only E484K/Q, F490S and S494P have been assessed phenotypically to date. Considering all variants detected at positions E484, F490 and S494, 9.2% (9/98) and 6.1% (6/98) of participants in the 700 mg bamlanivimab arm harbored such a variant post-baseline at ≥15% and ≥50% allele fractions, respectively, compared with 8.2% (8/97) and 4.1% (4/97), respectively, of participants in the placebo arm. Most of these variants were first detected on Day 7 following treatment initiation and many were detected only at a single time point (700 mg arm: 5/9 and 2/6 at ≥15% and ≥50% allele fractions, respectively; placebo arm: 8/8 and 4/4, respectively). For the 700 mg bamlanivimab arm, these variants were detected more frequently in high-risk participants (14.0% [6/43] and 9.3% [4/43] at ≥15% and ≥50% allele fractions, respectively, vs 2.4% [1/41] and 0% [0/41], respectively, in the placebo arm). The clinical relevance of these findings is not known.

It is possible that bamlanivimab resistance-associated variants could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

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

In toxicology studies in rats, bamlanivimab had no adverse effects when administered intravenously. Non-adverse increases in neutrophils were observed.

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

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

In Vivo Efficacy Pharmacology

Prophylactic administration of bamlanivimab to female Rhesus macaques (n=3 or 4 per group) resulted in 1 to 4 log₁₀ decreases in viral load (genomic RNA) and viral replication (sub-genomic RNA) in bronchoalveolar lavage samples relative to control animals, but less of an impact on viral RNA in throat and nasal swabs following SARS-CoV-2 inoculation. The applicability of these findings to a prophylaxis or treatment setting is not known.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

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

The data supporting this EUA are based on an interim analysis from Part A of BLAZE-1 that occurred after all enrolled subjects completed at least Day 29 of the trial. BLAZE-1 Part A is a randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). BLAZE-1 enrolled adult patients who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects were treated with a single infusion of bamlanivimab (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) or placebo (N=156).

At baseline, median age was 45 years (with 12% of subjects aged 65 or older); 55% of subjects were female, 88% were White, 44% were Hispanic or Latino, and 6% were Black; 44% of subjects were considered high risk (as defined in Section 2). Subjects had mild (76%) to moderate COVID-19 (24%); the mean duration of symptoms was 5 days; mean viral load by cycle threshold (CT) was 24 at baseline. The baseline demographics and disease characteristics were well balanced across bamlanivimab and placebo treatment groups.

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

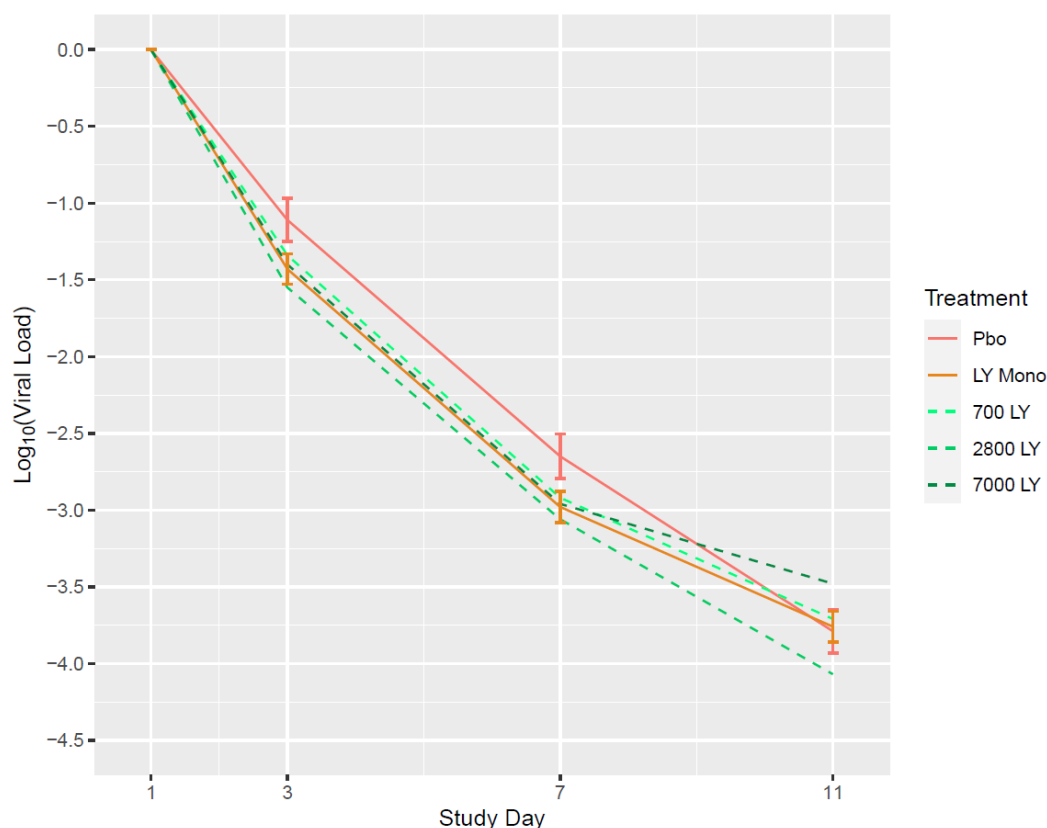


Figure 1: SARS-CoV-2 viral load change from baseline by visit.

While viral load was used to define the primary endpoint in this Phase 2 trial, the most important evidence that bamlanivimab may be effective came from the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. A lower proportion of bamlanivimab-treated subjects progressed to COVID-19-related hospitalization or emergency room visits compared to placebo-treated subjects (Table 3). Results for this endpoint were suggestive of a relatively flat dose-response relationship.

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

Treatment	N ^a	Events	Proportion of Subjects %
Placebo	156	9	6%
bamlanivimab 700 mg	101	1	1%
bamlanivimab 2800 mg	107	2	2%
bamlanivimab 7000 mg	101	2	2%
All bamlanivimab doses	309	5	2%

^a N = number of treated patients in analysis.

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

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

Treatment	N ^a	Events	Proportion of Subjects %
Placebo	69	7	10%
bamlanivimab 700 mg	46	1	2%
bamlanivimab 2800 mg	46	1	2%
bamlanivimab 7000 mg	44	2	5%
All bamlanivimab doses	136	4	3%

^a N = number of treated patients in analysis.

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

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Bamlanivimab injection, 700 mg/20 mL (35 mg/mL), is a sterile, preservative-free clear to slightly opalescent and colorless to slightly yellow to slightly brown solution supplied as one single-dose vial per carton.

NDC 0002-7910-01

Storage and Handling

Bamlanivimab is preservative-free. Discard unused portion.

Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

DO NOT FREEZE, SHAKE, OR EXPOSE TO DIRECT LIGHT.

Solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted bamlanivimab infusion solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature (20°C to 25°C [68°F to 77°F]) for up to 7 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature prior to administration.

20 PATIENT COUNSELING INFORMATION

Patients treated with bamlanivimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines. Also see Fact Sheet for Patients, Parents and Caregivers.

21 CONTACT INFORMATION

For additional information visit:

www.bamlanivimab.com

If you have questions, please contact:

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

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Eli Lilly and Company, Indianapolis, IN 46285, USA

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Fact Sheet for Patients, Parents and Caregivers

Emergency Use Authorization (EUA) of Bamlanivimab for Coronavirus Disease 2019 (COVID-19)

You are being given a medicine called **bamlanivimab** for the treatment of coronavirus disease 2019 (COVID-19). This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking bamlanivimab, which you may receive.

Receiving bamlanivimab may benefit certain people with COVID-19.

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

What is COVID-19?

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

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?

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

What is bamlanivimab?

Bamlanivimab is an investigational medicine used for the treatment of COVID-19 in non-hospitalized adults and adolescents 12 years of age and older with mild to moderate symptoms who weigh 88 pounds (40 kg) or more, and who are at high risk for developing severe COVID-19 symptoms or the need for hospitalization. Bamlanivimab is investigational because it is still being studied. There is limited information known about the safety or effectiveness of using bamlanivimab to treat people with COVID-19.

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

What should I tell my healthcare provider before I receive bamlanivimab?

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

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

How will I receive bamlanivimab?

- Bamlanivimab is given to you through a vein (intravenous or IV) for at least 1 hour.
- You will receive one dose of bamlanivimab by IV infusion.

What are the important possible side effects of bamlanivimab?

Possible side effects of bamlanivimab are:

- Allergic reactions. Allergic reactions can happen during and after infusion with bamlanivimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions:

fever, chills, nausea, headache, shortness of breath, low blood pressure, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, and dizziness.

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

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

It is possible that bamlanivimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, bamlanivimab may reduce your body's immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

What other treatment choices are there?

Like bamlanivimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to <https://www.covid19treatmentguidelines.nih.gov/> for information on the emergency use of other medicines that are not approved by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials you may be eligible for.

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

What if I am pregnant or breastfeeding?

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

How do I report side effects with bamlanivimab?

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

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

How can I learn more?

- Ask your healthcare provider
- Visit www.bamlanivimab.com
- Visit <https://www.covid19treatmentguidelines.nih.gov/>
- Contact your local or state public health department

What is an Emergency Use Authorization (EUA)?

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

Bamlanivimab has not undergone the same type of review as an FDA-approved or cleared product. The FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, and available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that the product meets certain criteria for safety, performance, and labeling and may be effective in treatment of patients during the COVID-19 pandemic. All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic.

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

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