Emergency Use Authorization (EUA) for bamlanivimab 700 mg and etesevimab 1,400 IV

Center for Drug Evaluation and Research (CDER) Memorandum on Fact Sheet Update

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	94
Date of Memorandum	May 14, 2021
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
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Integrated Review Completion Date	February 9, 2021
Proprietary Name	n/a
Established Name/Other names used during development	bamlanivimab (LY3819253, LY-CoV555) and etesevimab (LY3832479, LY-CoV016)
Dosage Forms/Strengths	Bamlanivimab 700 mg and etesevimab 1400 mg IV
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibody (mAb)
Intended Use or Need for EUA	mild to moderate COVID-19
Intended Population(s)	treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death

I. Issue Summary

This memorandum provides a brief summary of the proposed changes to the Health Care Provider Fact Sheets and Patient Fact Sheets for EUA 94 for bamlanivimab and etesevimab. The following are the most recent major changes are made to the version authorized on May 14, 2021.

RECENT MAJOR CHANGES SINCE MARCH 2021

- Definition of High Risk for Disease Progression (Box and Section 2.1) – definition has been expanded to include additional medical conditions and other factors.
- Dosage and Administration, Dosage (Section 2.2) – removal of rationale for authorized dose because Phase 3 data have confirmed the authorized dose.
- Overall Safety Summary, Clinical Trials Experience (Section 6.1) – updated to integrated clinical trial safety analyses focused on adverse reactions and most common treatment-emergent adverse events
- Antiviral Resistance (Box and Section 15) – addition of information on susceptibility of SARS-CoV-2 variants to bamlanivimab and etesevimab (Table 3 and Table 4).
- Clinical Trial Results and Supporting Data for EUA, Mild to Moderate COVID-19 (BLAZE-1) (Section 18.1) – addition of Phase 3 data for the authorized dose.

II. Rationale and Revisions to EUA Fact Sheets

Definition of High Risk for Disease Progression (Box and Section 2.1)

On January 14, 2021, Eli Lilly and Company (Lilly) requested to modify the definition of high risk for progressing to severe COVID-19 and/or hospitalization for bamlanivimab 700 mg and etesevimab 1400 mg administered together (EUA 94). Lilly has reported that prescribers and community stakeholders have inquired to broadening the high risk criteria to include some other risk groups thought to have higher risk for severe disease. Subgroup analyses were then requested from Lilly to determine relative efficacy of bamlanivimab and etesevimab for people in certain high risk groups. In general, favorable trends were demonstrated for the primary outcomes (hospitalization or death) for the various subgroups of subjects enrolled in the BLAZE-1 trial; these analyses support an expansion of high risk criteria (Table 1). In some subgroups, the number of events was small and therefore it was challenging to make definitive conclusions. Indeed, the BLAZE-1 trial was not powered to assess differences for individual subgroups or in a collection of subgroups. In addition, approximately half of individual trial participants had two or more high risk conditions, placing them at potentially even higher risk of developing severe disease.

Table 1: Subgroup Analysis of Outcomes (Hospitalization or Death) for High Risk Factors From BLAZE-1 (Phase 2 and Phase 3 data)

Risk Factor	Placebo N=932	BAM 2800 and ETE 2800 N=630	BAM 700 and ETE 1400 N=511	Combined BAM and ETE N=1141	Combined Treatment Effect (% reduction compared to placebo)
Age 12-17 and BMI **≥85th** percentile for their age and gender based on CDC growth charts	0/8 (0%)	0/4 (0%)	0/8 (0%)	0/12 (0%)	NE
Asthma (moderate to severe)	1/27 (3.7%)	0/25 (0%)	0/15 (0%)	0/40 (0%)	100%
BMI **≥35**	36/409 (8.8%)	4/265 (1.5%)	0/222 (0%)	4/487 (0.8%)	91%
Cancer	2/39 (5.1%)	1/31 (3.2%)	0/28 (0%)	1/59 (1.7%)	67%
Cerebrovascular disease	0/15 (0%)	1/12 (8.3%)	0/12 (0%)	1/24 (4.2%))	NE
Chronic kidney disease	4/27 (14.8%)	1/12 (8%)	0/6 (0%)	1/18 (5.6%)	63%
Congenital heart disease	1/3 (33%)	0/1 (0%)	0/2 (0%)	0/3 (0%)	100%
COPD	6/110 (5.5%)	1/96 (1%)	1/73 (1%)	2/169 (1.2%)	78%
Cystic Fibrosis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	NE
Diabetes	19/211 (9%)	6/161 (3.7%)	1/139 (0.7%)	7/300 (2.3%)	74%
Down Syndrome	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	NA
Heart Conditions (eg HF, CAD, cardiomyopathy)	11/72 (15.3%)	4/49 (8.2%)	1/51 (2%)	5/100 (5%)	67%
Hypertension	33/410 (8%)	7/269 (2.6%)	3/244 (1.2%)	10/513 (1.9%)	76%
Immunocompromised state from solid organ txplnt	0/4 (0%)	0/7 (0%)	0/1 (0%)	0/8 (0%)	NE
Immunocompromised state from blood or bone marrow txplnt, immune deficiencies, HIV, use of corticosteroids, or use of other immune awakening medicines	0/10 (0%)	1/11 (9.1%)	0/8 (0%)	1/19 (5.3%)	NE
Immunosuppressive disease	0/10 (0%)	1/11 (9.1%)	0/8 (0%)	1/19 (5.3%)	NE
Immunosuppressive treatment	2/49 (4.1%)	0/26 (0%)	1/28 (3.6%)	1/54 (1.9%)	55%
Liver disease	2/17 (11.8%)	1/11 (9.1%))	0/12 (0%)	1/23 (4.3%)	63%
Medically-related technological dependence	0/1 (0%)	0/0 (0%)	0/1 (0%)	0/1 (0%)	NE
Neurodevelopmental disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	NE
Neurologic conditions	3/11 (27.3%)	0/6 (0%)	0/2 (0%)	0/8 (0%)	100%
Obesity (BMI **≥30)**	44/571 (7.7%)	6/369 (1.6%)	3/306 (0.9%)	9/675 (1.3%)	83%
Overweight (BMI 25-30 kg/m2)	9/203 (4.4%)	3/148 (2%)	1/124 (0.8%)	4/272 (1.5%)	67%
Pregnancy	0/0 (0%)	0/1 (0%)	0/0 (0%)	0/1 (0%)	NE
Sickle cell disease	0/1 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	NE
Smoking	16/227 (7%)	1/157 (0.6%)	2/137 (1.5%)	3/294 (1%)	86%

Source: Regulatory Response: Updated Tables for High Risk Criteria, dated March 22, 2021.
Abbreviations: BMI = body mass index, HF = heart failure, CAD = coronary artery disease, NE = not evaluable

We note that CDC's categorization of conditions and other factors that confer high risk of progression to severe COVID-19, including hospitalization or death, has evolved since the pandemic began and is, at present, quite broad. Based on the antiviral mechanism of action which is independent of the specific risk factor or medical condition, it is expected that any patient with risk factors for progression to severe COVID-19 could potentially derive benefit from treatment with monoclonal antibodies directed against the virus. Based on the benefit/risk

assessment and a low number needed to treat to prevent one hospitalization or death observed in the Phase 3 trial (estimated number needed to treat of 21 based on the data from the bamlanivimab 2800 mg and etesevimab 2800 mg dose), we have determined that additional groups deemed to be at high risk for progression of COVID-19 will likely benefit from treatment with bamlanivimab and etesevimab together.

As such, we have now broadened the current definition of high risk for progression to severe disease to include 11 specific medical conditions or factors in the Fact Sheet for Health Care Providers, but have noted that the authorized use of bamlanivimab and etesevimab under the EUA would not be limited to this list. A webpage link to the CDC website that provides a more extensive list and discussion of medical conditions or factors that are associated with increased risk of progression to severe COVID-19 is also included, which allows health care providers to access a more comprehensive list (including the data that supports the list) that allows healthcare providers the ability to make a medical judgement for the benefit risk for the individual they are treating; and, the list can be updated in real time, should the CDC identify additional medical conditions or factors deemed to be high risk of progression to severe COVID-19. With these changes, healthcare providers may now consider the benefit risk for an individual patient based on the specified list in the Fact Sheet for Health Care Providers and the CDC curated website that designates high risk medical conditions or factors, within the specified authorization of use.

This amended language now appears in the Fact Sheet for Health Care Providers as follows:

> The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:
>
> - Older age (for example age ≥65 years of age)
> - Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
> - Pregnancy
> - Chronic kidney disease
> - Diabetes
> - Immunosuppressive disease or immunosuppressive treatment
> - Cardiovascular disease (including congenital heart disease) or hypertension
> - Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
> - Sickle cell disease
> - Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
> - Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))
>
> Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Changes were also made to the Fact Sheet for Patients, Parents and Caregivers to reflect the expansion of the high risk criteria. These changes are included in bold:

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

Dosage and Administration, Dosage (Section 2.2) and Clinical Trial Results and Supporting Data for EUA, Mild to Moderate COVID-19 (BLAZE-1) (Section 18.1)

The authorized dose of bamlanivimab 700 mg and etesevimab 1400 mg administered together was selected based on analyses of data available at that time. For the EUA request, Lilly had submitted data demonstrating that a dosage of bamlanivimab 2,800 mg and etesevimab 2,800 mg administered together reduced COVID-19 related hospitalizations and deaths in addition to significantly reducing viral load relative to placebo. In addition, bamlanivimab 700 mg and etesevimab 1,400 mg administered together had similar antiviral activity to a dosage of bamlanivimab 2,800 mg and etesevimab 2,800 mg administered together, which was also supported by in vitro data and pharmacokinetic/pharmacodynamic (PK/PD) modeling. Bamlanivimab 700 mg and etesevimab 1,400 mg administered together was therefore expected to have a similar clinical effect to a dosage of bamlanivimab 2,800 mg and etesevimab 2,800 mg administered together based on nonclinical, clinical and virologic data. Given this, bamlanivimab 700 mg and etesevimab 1,400 mg administered together was ultimately authorized on February 9, 2021.

Additional Phase 3 data to support the dose of bamlanivimab 700 mg and etesevimab 1400 mg were submitted to the Division in March, 2021. These data demonstrated treatment with bamlanivimab 700 mg and etesevimab 1,400 mg resulted in a significant difference in the proportion of subjects with COVID-19 related hospitalization or death in individuals at high risk for disease progression as defined by the trial protocol. These results validated the method used, as well as the selection of the authorized dose, when the EUA was authorized. Because phase 3 clinical trial data are now available demonstrating the efficacy and safety of bamlanivimab 700 mg and etesevimab 1,400 mg, the rationale for the selection of the authorized dosage has been removed from Section 2.2.

These additional Phase 3 data are now included in Section 18. These data demonstrate that bamlanivimab 700 mg and etesevimab 1,400 mg can reduce COVID-19 related hospitalization and death and result in reductions in viral load compared to placebo. In addition, participants treated with bamlanivimab 700 mg and etesevimab 1,400 mg had a shorter time to sustained symptom resolution compared to participants treated with placebo.

The following wording is now included:

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

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

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

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29. Events occurred in 15 subjects treated with placebo (6%) as compared to 4 events in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together (0.8%) [$p<0.0001$], an 87% reduction. There were 4 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together ($p=0.01$).

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

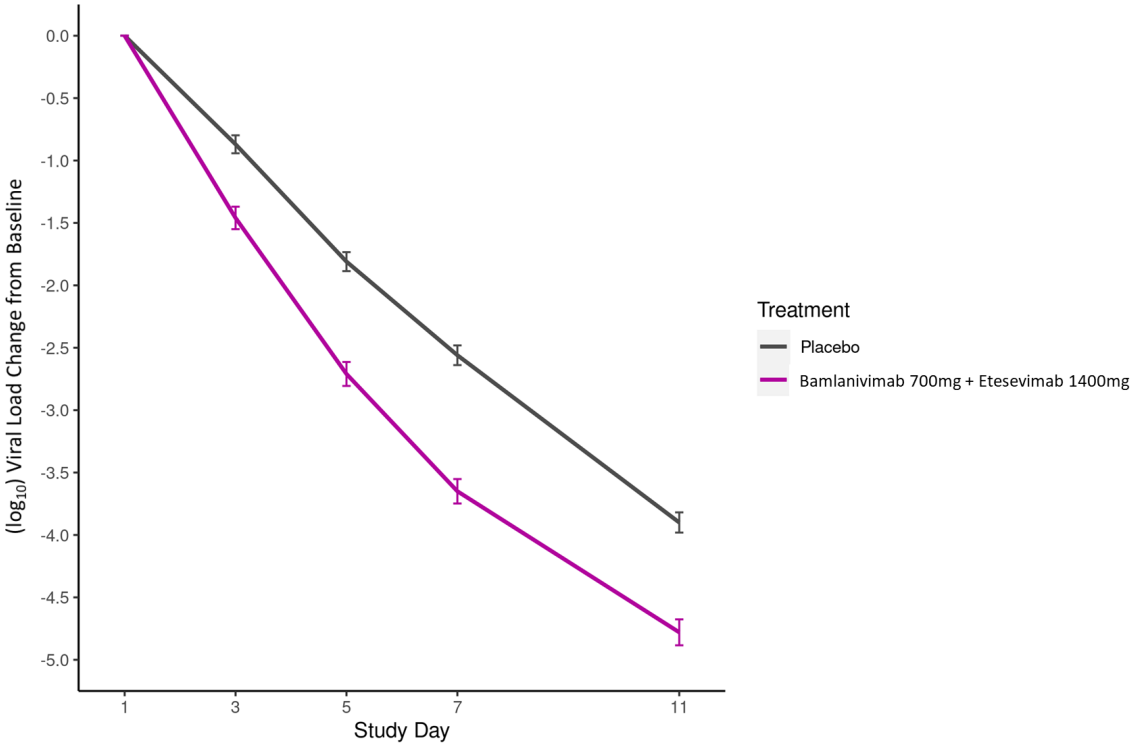

Figure 2: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Phase 3 Portion of BLAZE-1 (700 mg bamlanivimab and 1,400 mg etesevimab).

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

Given that clinical trial data are now available for the authorized dose, data from the Phase 3 portion of BLAZE-1 that assessed the efficacy and safety of bamlanivimab 2,800 mg and etesevimab 2,800 mg are now viewed by the Division as supportive in nature. As such, this portion of Section 18 has now been edited and streamlined, and now only reflects demographic information of trial participants and the results for the primary endpoint. This section is now as follows:

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

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

were also enrolled in the trial (4 [0.8%] were treated with bamlanivimab and etesevimab and 7 [1.4%] were treated with placebo), and met high-risk criteria as defined in the trial protocol.

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

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

Overall Safety Summary, Clinical Trials Experience (Section 6.1)

On March 26, 2021, Lilly proposed changes to Section 6 of the Fact Sheet for Health Care Providers that reflected an integrated safety analysis of participants in Trail PYAB (BLAZE-1) and PYAH (BLAZE-4). Potential hypersensitivity events were evaluated by examining preferred terms from 3 subject matter queries (SMQs): anaphylaxis, hypersensitivity, and angioedema. The description of infusion-related reactions includes all the infusion-related reaction terms except for the non-specific terms of cough, which also may be associated with the treated disease, and infusion site rash.

As a result of these analyses, Section 6.1 now focuses on two adverse drug reactions, anaphylaxis and infusion-related reactions, and provides frequencies based on integrated clinical trial safety data for participants who received the authorized dose of bamlanivimab 700 mg and etesevimab 1400 mg administered together in BLAZE-1 and BLAZE-4.

A separate analysis was performed to evaluate the most commonly reported treatment-emergent adverse events based on study-size adjusted percentages.

Section 6.1 is now as follows:

The safety of bamlanivimab administered with etesevimab is primarily based on exposure of approximately 1400 ambulatory (non-hospitalized) subjects who received doses of bamlanivimab and etesevimab together, at the recommended dose or higher, in BLAZE-1 and BLAZE-4. BLAZE-1 is an ongoing Phase 2/3, randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19. In the Phase 3 portion of the trial, enrolled participants had at least one risk factor for the development of severe COVID-19 illness. BLAZE-4 is an ongoing Phase 2, randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab for the treatment of subjects with mild to moderate COVID-19. Subjects ≥65 years old or with BMI ≥35 were excluded from enrollment. In clinical trials, approximately 4,000 subjects have received bamlanivimab (either alone or with etesevimab) at doses ranging from 700 to 7,000 mg. Bamlanivimab and etesevimab at the authorized doses of 700 mg and 1,400 mg have been administered together to approximately 800 subjects in clinical trials *[see Clinical Pharmacology (14.2)]*.

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

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

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

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

Antiviral Resistance (Box and Section 15) –

Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing, with monthly updates provided by Lilly. Updated neutralization data using pseudotyped virus-like particles (VLPs) have been added to Table 3. Changes in susceptibility of bamlanivimab and etesevimab were assessed using pseudotyped VLPs expressing consensus spike protein sequences for B.1.351, P.1, and B.1.427/B.1.429, as well as for key substitutions for variants of concern. Neutralization data using authentic virus are included in Table 4.

Clinical interpretations of these data were added to the fact sheet. While it is unclear as to how neutralization data correlate with clinical outcomes, it is noted that the available information indicates that bamlanivimab and etesevimab may be active against variants within the B.1.526 lineage, though limited clinical data are available due to the paucity of subjects infected with the B.1.526 variant. One hundred and thirty-four participants in BLAZE-1 were likely infected with the B.1.427/B.1.429 variant (n=50 in placebo arm, 84 in BAM+ETE arm), based on detection of L452R and other substitutions at baseline. Similar virologic outcomes were observed in participants infected with the B.1.427/B.1.429 variant as for participants infected with variants sensitive to bamlanivimab providing preliminary evidence indicating that bamlanivimab and etesevimab have activity against this variant in the clinic.

An update was also provided to the genotypic and phenotypic testing that are ongoing to monitor for potential bamlanivimab and etesevimab-resistance associated spike variations in circulation, as well as clinical trial samples analyzed for treatment emergent variants.

The following information now appears in the Antiviral Resistance portion of Section 15, with new information highlighted in bold:

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab and/or etesevimab **(Table 3).** Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

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

Q493R substitutions, which had reduced susceptibility of 17-fold, 22-fold, and >100-fold, respectively in a **pseudotyped VLP assay.**

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

Bamlanivimab alone and bamlanivimab and etesevimab together retained activity against a **SARS-CoV-2 B.1.1.7 lineage (UK origin) virus and related pseudotyped VLPs expressing** del69-70 + N501Y found in the B.1.1.7 variant. **Pseudotyped VLPs** expressing spike protein from the B.1.351 lineage (South Africa origin) or substitutions K417N + E484K + N501Y found in this lineage had reduced susceptibility to bamlanivimab and etesevimab together of **215-fold or >45-fold, respectively**, and **pseudotyped VLPs expressing spike protein from the P.1 lineage (Brazil origin)** or K417T + E484K + N501Y found in the P.1 lineage had reduced susceptibility to bamlanivimab and etesevimab together of **>46-fold** or >511-fold, **respectively**. **Pseudotyped VLPs** expressing spike protein from the B.1.427/B.1.429 lineages (California origin) or the L452R substitution found in this lineage, maintained activity for etesevimab but showed reduced susceptibility to bamlanivimab and etesevimab together of **9-fold or 15-fold,** respectively (Table 3).

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

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	K417N + E484K + N501Y	**215**[c]
P.1 (Brazil origin)	K417T + E484K + N501Y	**>46**[c]
B.1.427/B.1.429 (California origin)	L452R	**9**[d]
B.1.526 (New York origin)[e]	E484K	**31**

[a] For variants with more than one substitution of concern, only the substitution(s) with the greatest impact on activity is(are) listed. **For B.1.351, P.1 and B.1.427/B.1.429, spike variants reflective of the consensus sequence for the lineage were tested.**

[b] No change: <5-fold reduction in susceptibility.

[c] Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage. No activity observed at the highest concentration tested for the P.1 variant.

[d] **Etesevimab retains activity against this variant.**

[e] **Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions**, and not all isolates contain the E484K substitution (as of February 2021). **This assay was conducted using pseudotyped VLPs with the E484K substitution only.**

Table 4: Authentic[a] SARS-CoV-2 Neutralization Data for Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

Lineage with Spike Protein Substitution	Key Substitution Tested[b]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[c]
B.1.526 (New York origin)[d]	E484K	10.5

[a] The B.1.1.7 variant was assessed using cell culture-expanded virus; the B.1.526/E484K substitution was assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate).
[b] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed.
[c] No change: <5-fold reduction in susceptibility.
[d] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021). This assay was conducted using recombinant SARS-CoV-2 with the E484K substitution only.

Due to the lack of pseudotyped VLP neutralization activity of both bamlanivimab and etesevimab against the substitutions in B.1.351 (South Africa origin) and P.1 (Brazil origin), it is unlikely that bamlanivimab and etesevimab together will be active against these variants.

It is unclear how small reductions in susceptibility to bamlanivimab and etesevimab seen in authentic or recombinant SARS-CoV-2 or pseudotyped VLP assays correlate with clinical outcomes. Bamlanivimab alone does not retain activity against variants with E484K. SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the E484K substitution present in the B.1.526 lineage (New York origin) retained activity to etesevimab alone but showed reduced susceptibility to bamlanivimab and etesevimab together of 10-fold (Table 4). Available nonclinical and clinical PK data indicate that etesevimab at the authorized dose may retain activity against the B.1.526 variant clinically, although only very limited data are currently available from patients infected with this variant in clinical trials. Preliminary clinical evidence indicates that the administration of bamlanivimab and etesevimab together result in similar viral load reductions in participants infected with the L452R variant (California origin) as observed in those who were infected with bamlanivimab-sensitive strains. Of the 134 participants infected with the L452R variant at baseline in the Phase 3 portion of BLAZE-1, 3 of the 50 individuals treated with placebo (6%) and 1 of the 84 participants treated with bamlanivimab 700 mg and etesevimab 1,400 mg (1%) were hospitalized (p=0.15).

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab- and etesevimab-resistance associated spike variations in clinical trials. **Analysis of baseline samples show that 9.8% (163/1662) of clinical trial patients were infected with viral variants containing single amino acid substitutions at positions associated with reduced susceptibility to either bamlanivimab or etesevimab as predicted by pseudotyped VLP neutralization assays. Only 1 patient was infected with a variant (E484G) that was predicted to have reduced susceptibility to both bamlanivimab and etesevimab.**

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

- **In the Phase 3 portion of BLAZE-1, treatment-emergent variants were observed in 7.1% (30/425) of patients treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together, in 11.5% (6/52) of patients treated with bamlanivimab 700 mg and etesevimab 1,400 mg together, and in 3.7% (17/462) of patients treated with placebo.**
- **In patients treated with bamlanivimab and etesevimab together, substitutions detected in one or more patients included ones with reduced susceptibility (≥5-**

fold) to bamlanivimab only: L452R, E484K, G485V, and S494P; and ones with reduced susceptibility to etesevimab only: D405Y, K417N, D420N, N460T, and N501T. While these variants had reduced susceptibility to either bamlanivimab OR etesevimab compared to wild-type in a pseudotyped VSV VLP assay they still retained susceptibility to the other antibody in the combination.

- **There were also observations of variants with reduced susceptibility (≥5-fold) to both bamlanivimab and etesevimab: F490L (n=3; 13-fold reduction) and Q493K/R (n=2; >34-fold [Q493K] and >100-fold [Q493R] reductions) out of a total of 579 patients treated with bamlanivimab and etesevimab together.**
- **Additional treatment-emergent substitutions in patients treated with bamlanivimab and etesevimab together, with no phenotypic data, include D405del, D420Y, N460I, G485D, and S494L. The impact of these substitutions is not currently known.**

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

Additional Changes

In addition to the recent major changes that are reviewed above, updates were made in Section 11 related to use in specific populations. Sections 11.3 and 14.3, now state that data from 10 adolescents have demonstrated that plasma exposures are comparable to what has been observed in adult patients at the authorized dose. In Section 11.4, the numbers of patients who were older than 65 and 75 years of age in BLAZE-1 were added.

Regulatory Conclusion:

Collectively, the revisions to the Fact Sheets detailed above do not alter the analysis of benefits and risks that underlies the initial authorization of EUA 94.

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/s/

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