Emergency Use Authorization (EUA) for

bamlanivimab 700 mg and etesevimab 1400 mg 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	March 17, 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 (COVID19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

I. Issue Summary

Emergency Use Authorization (EUA) 94 currently authorized the emergency use of bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

SARS-CoV-2 is evolving over time, resulting in genetic variation in the population of circulating viral strains. Some variants can cause resistance to one or more of the mAb therapies authorized to treat COVID-19. Since the time of authorization of EUA 94, viral variants of SARS-CoV-2 have been noted to be circulating in the United States.

In response, the Division requested that Lilly conduct cell culture neutralization studies to assess the activity of bamlanivimab and etesevimab against these variants, and/or amino acid substitutions found in these variants. The Sponsor provided pseudovirus data for spike protein substitutions found in variants B.1.1.7 (UK origin), B.1.351 (South Africa origin), P.1 (Brazil origin), B.1.427/B.1.429 (California origin), and B.1.526 (New York origin). Following review of the data indicating that bamlanivimab and etesevimab administered together would likely have reduced or lose activity against some of the circulating variants of interest and variants of concern, changes were made to the Fact Sheet for Healthcare Providers to inform healthcare providers of this issue.

This memorandum provides a brief summary of changes made to the February 9, 2021 authorized Fact Sheet for Healthcare Providers for EUA 94 for bamlanivimab and etesevimab.

II. Summary of Revision to EUA Fact Sheets

Based on review of the available pseudovirus data, the following summarizes the changes were made to the Fact Sheet for Healthcare Providers authorized on March 18, 2021:

RECENT MAJOR CHANGES

- Antiviral Resistance (Box and Section 15) - addition of information on susceptibility of SARS-CoV-2 variants to bamlanivimab alone (Table 3) — Revised 03/2021

Box Section:
Updates were added to the box to communicate that healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area when considering treatment options. The text is as follows:

> Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health care providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Antiviral Resistance (Section 15):
Updates were added to this section to reiterate that treatment failure due to variants is possible and that healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area when considering treatment options. Non-clinical data, as well as a table highlighting pseudovirus data, were also added. Substantive additions to this section are shown in bold:

> There is a potential risk of treatment failure due to the development of viral variants that are resistant to both bamlanivimab and etesevimab. **Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.**
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> Resistant variants were identified using directed evolution of the spike protein and serial passage in cell culture of SARS-CoV-2 in the presence of bamlanivimab or etesevimab individually. Resistant variants were not identified when bamlanivimab and etesevimab were tested together using the same methodology. Viral variants identified in these studies that had reduced susceptibility to bamlanivimab included spike protein amino acid substitutions E484D/K/Q, F490S, Q493R, and S494P, and variants that had reduced susceptibility to etesevimab included substitutions K417N, D420N, and N460K/S/T. Neutralization assays using SARS-CoV-2, vesicular stomatitis virus-based pseudovirus, or binding assessment if pseudovirus construction was unsuccessful (E484D), confirmed reductions in susceptibility to the selecting antibody. Retention of susceptibility to the other antibody alone was observed, with the exception of the Q493R substitution. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of those with E484K, E484Q, and Q493R substitutions, which had reduced susceptibility of **17**-fold, 22-fold, and >100-fold, respectively in a pseudovirus assay.
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> Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing. Pseudoviral evaluation of amino acid substitutions identified in global surveillance showed that the V483A substitution reduced susceptibility to bamlanivimab 48-fold, but activity was maintained with etesevimab, and with bamlanivimab and etesevimab together. N501Y and N501T substitutions reduced susceptibility to etesevimab approximately 5-fold and 20-fold, respectively. Activity against variants with N501Y or N501T substitutions was maintained with bamlanivimab alone, and with bamlanivimab and etesevimab together.

Bamlanivimab alone and bamlanivimab and etesevimab together retained activity against pseudovirus expressing del69-70 + N501Y found in the B.1.1.7 variant (UK origin). **Pseudovirus 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 >45-fold, and pseudovirus expressing K417T + E484K + N501Y found in the P.1 lineage (Brazil origin) had reduced susceptibility to bamlanivimab and etesevimab together of >511-fold. Pseudovirus expressing spike protein from the B.1.427/B.1.429 lineages (California origin), or the L452R substitution found in this lineage, had reduced susceptibility to bamlanivimab and etesevimab together of 7.7-fold or 7.4-fold, respectively (Table 3).**

Table 3: Pseudovirus 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	>45[c]
P.1 (Brazil origin)	K417T + E484K + N501Y	>511[c]
B.1.427/B.1.429 (California origin)	L452R	7.4
B.1.526 (New York origin)[d]	E484K	17

[a] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed.
[b] No change: <5-fold reduction in susceptibility.
[c] No activity observed at the highest concentration tested. Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage.
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021)

It is not known how pseudovirus data correlate with clinical outcomes. Given the similarities between the substitutions in B.1.351 and P.1, it is unlikely that bamlanivimab and etesevimab together will be active against these variants.

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab- and etesevimab-resistance associated spike variations in clinical trials. Detection of phenotypically confirmed bamlanivimab- or etesevimab-resistant variants in baseline samples were observed at a frequency of 0% (0/14) in the Phase 1 clinical study PYAA and 0.4% (2/523) in clinical study BLAZE-1.

In BLAZE-1, treatment-emergent variants were detected at spike protein amino acid positions K417, D420, N460, E484, F490 and S494, and included K417N, D420N, N460T, E484A/D/G/K/Q/V, F490L/S/V and S494L/P substitutions. Only K417N, D420N, N460T, E484D/K/Q, F490S and S494P have been assessed phenotypically to date. At positions K417, D420, N460, E484, F490 and S494, 9.2% (9/98) and 6.1% (6/98) of participants in the 700 mg bamlanivimab arm harbored such a variant post-baseline at ≥15% and ≥50% allele fractions, respectively. For subjects treated with bamlanivimab and etesevimab, the variant

frequencies were 3.9% (4/102) and 0% (0/102) at ≥15% and ≥50% allele fractions, respectively. The majority of the variants were first observed on Day 7 following treatment initiation. Some of the variants were detected in individuals at more than one time point in the 700 mg bamlanivimab arm: 4/9 and 4/6 at ≥15% and ≥50% allele fractions, respectively; however, in the bamlanivimab and etesevimab arm there were no such observations (0/4 at ≥15% allele fraction). When the genotypic analysis was restricted to high-risk participants, the 700 mg bamlanivimab arm showed a 14.0% (6/43) and 9.3% (4/43) variant frequency for the ≥15% and ≥50% allele fractions, respectively, and no variants were detected in the bamlanivimab and etesevimab arm. The clinical relevance of these findings is not known.

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

Other minor updates were completed for corrections of formatting or for clarity.

Regulatory Conclusion:

FDA is working closely with the sponsors of the mAb EUAs to understand the potential impact of a variant on the effectiveness of the currently authorized mAb therapies. FDA is also working with the Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response, the CDC, and other government organizations to closely monitor the situation.

Based on the available data, revisions were made to the Fact Sheet for Healthcare Providers to provide updates to the antiviral resistance information as detailed above.

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/s/

NATALIE M PICA
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WENDY W CARTER
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