Emergency Use Authorization (EUA) for bamlanivimab 700mg 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)	90
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	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 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) 90 currently authorizes the emergency use of bamlanivimab alone 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 90, 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 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 alone would likely 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 90 for bamlanivimab alone.

II. Summary of Revision to EUA Fact Sheets

Based on review of the available pseudovirus data, the following 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. Consideration of the use of other monoclonal antibodies is also communicated. 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.

The use of alternative authorized monoclonal antibodies that are expected to retain activity against circulating viral variants may reduce the potential risk of treatment failure should a patient be infected with a SARS-CoV-2 viral variant that is resistant to bamlanivimab alone.

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 SARS-CoV-2 variants that are resistant to bamlanivimab. **Prescribing healthcare providers should consider the prevalence of bamlanivimab resistance variants in their area, where data are available, when considering treatment options.**

Non-clinical studies using serial passage of SARS-CoV-2 and directed evolution of the spike protein identified amino acid substitutions E484**D**/K/**Q**, F490S, Q493R and S494P, in the spike protein receptor binding domain. These substitutions conferred reduced susceptibility to bamlanivimab as determined in neutralization assays using SARS-CoV-2 (F490S and S494P: >485-fold and >71-fold reduction, respectively), **vesicular stomatitis virus-based pseudovirus expressing spike protein with variant substitutions (all variants >100-fold reduction), and spike protein binding assessment if pseudovirus assessment was unsuccessful (E484D).**

Evaluation of susceptibility of variants identified through global surveillance and in subjects treated with bamlanivimab is ongoing. Pseudovirus harboring the E484K substitution had reduced susceptibility to bamlanivimab; this substitution is found in several lineages, including B.1.351 (South Africa origin), P.1 (Brazil origin) and B.1.526 (New York origin). In addition, pseudoviruses with the spike protein and concurrent spike substitutions present in the South African B.1.351 origin variant lineage (K417N + E484K + N501Y), and the Brazil origin P.1 variant lineage (K417T + E484K + N501Y) exhibited reduced susceptibility to bamlanivimab. Pseudovirus harboring the L452R and the spike protein from the California origin variant lineage B.1.427/B.1.429 exhibited reduced susceptibility to bamlanivimab. Bamlanivimab retained activity against pseudovirus expressing del69-70 + N501Y spike substitutions found in the UK origin B.1.1.7 variant lineage (Table 3).

Table 3: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab Alone

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)	E484K	>2,360[c]

P.1 (Brazil origin)	**E484K**	**>2,360[c]**
B.1.427/B.1.429 (California origin)	**L452R**	**>1,020[c]**
B.1.526 (New York origin)[d]	**E484K**	**>2,360[c]**

[a] For variants with more than one substitution of concern, only the one with the greatest impact on activity is listed.

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

[c] No activity was observed at the highest concentration tested. Bamlanivimab alone is 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; however, reduction in susceptibility of >1,000-fold indicates that there will likely be no activity of bamlanivimab alone against these variants.

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 the 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.

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/

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