Emergency Use Authorization (EUA) for bebtelovimab 175 mg

Center for Drug Evaluation and Research (CDER) Memorandum

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	111
Date of Memorandum	November 30, 2022
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)
Proprietary Name	n/a
Established Name/Other names used during development	bebtelovimab (LY-CoV1404)
Dosage Forms/Strengths	bebtelovimab 175 mg IV
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibody (mAb)
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg): • with positive results of direct SARS-CoV-2 viral testing, and • who are at high risk for progression to severe COVID-19, including hospitalization or death, and

	• for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate
Intended Population(s)	Adults and pediatric patients

Brief Summary of Key Regulatory Actions for EUA 111

On February 11, 2022, the U.S. Food and Drug Administration issued an EUA for bebtelovimab authorizing its use for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg), with positive results of direct SARS-CoV-2 viral testing, who are at high-risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate. As part of its authorization, the Agency included a Limitation on the Authorized Use (LOAU) for bebtelovimab stating that bebtelovimab would not be authorized for the treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.[1]

Beginning in September 2022, BQ.1 and BQ.1.1 were identified as Omicron subvariants. Because these subvariants harbor a K444T substitution, it was anticipated that bebtelovimab would not have neutralizing activity against these Omicron subvariants. The prevalence of both BQ.1 and BQ.1.1 have been increasing nationally since they were first identified.

On October 31, 2022, Lilly submitted pseudotyped virus-like particle (VLP) neutralization data for the Omicron subvariants, BQ.1 and BQ.1.1. Pseudotyped VLP data using full-length BQ.1 and BQ.1.1 spike protein showed significant reductions in bebtelovimab neutralizing activity, presumably due to the K444T substitution. This information was added to the Fact Sheet for Health Care Providers on November 4, 2022.

Recommendation

Consistent with section 564(g) of the Federal Food, Drug & Cosmetic Act, the Agency will periodically review the appropriateness and circumstances of each EUA.

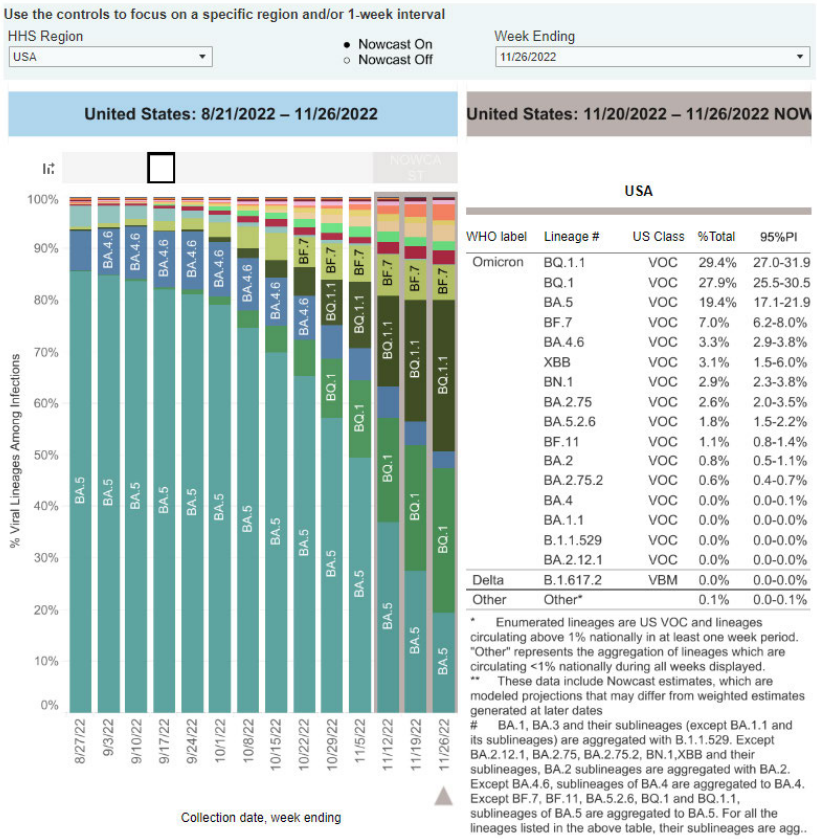
As part of its ongoing assessment of the circumstances and appropriateness of the EUA for bebtelovimab[2], FDA has continued to monitor for the emergence of viral variants of SARS-CoV-2 and their potential impact on the neutralization activity of the authorized monoclonal antibody therapy, including BQ.1 and BQ.1.1.

[1] In implementing this LOAU, FDA has and will continue to monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility (see, e.g., section 12.4 of authorized Fact Sheet for Health Care Providers), and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

[2] See section 564(g)(1) of the Federal Food, Drug & Cosmetic Act.

As stated above, BQ.1 and BQ.1.1 were identified as Omicron subvariants early in the Fall of 2022. At that time, there was significant uncertainty as to the specific prevalence of BQ.1 and BQ.1.1 in any particular state, territory, and U.S. jurisdiction. New data, however, are now available. Based on CDC's Nowcast model data as of November 26, 2022, it is estimated that BQ.1 and BQ 1.1 account for 29.4% (95% Prediction Interval [PI] 27-31.9%) and 27.9% (95% PI 25.5-30.5%) respectively, of the relative proportions of SARS-CoV-2 variants circulating in the United States and in U.S. territories and jurisdictions. All HHS regions[3] of the U.S., with the exception of Region 7, have cumulative point estimates above 50% for BQ.1 and BQ.1.1 Omicron subvariants; the cumulative point estimate for BQ.1 and BQ.1.1 in Region 7 is 34.8% (BQ.1: 16%, 95% PI 12.6-20%; BQ1.1: 18.8%, 15.2-23%).[4] Data show a sustained trend of increasing prevalence of BQ.1 and BQ1.1 Omicron subvariants across all the regions of the U.S.

Additionally, another Omicron subvariant, XBB, is circulating at low levels (3.1%, 95% PI 1.5-6%). Given that XBB harbors the spike protein V445P substitution, which on its own confers >850-fold reduction in susceptibility to bebtelovimab, it is expected that bebtelovimab will not be active against XBB.



USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BQ.1.1	VOC	29.4%	27.0-31.9
	BQ.1	VOC	27.9%	25.5-30.5
	BA.5	VOC	19.4%	17.1-21.9
	BF.7	VOC	7.0%	6.2-8.0%
	BA.4.6	VOC	3.3%	2.9-3.8%
	XBB	VOC	3.1%	1.5-6.0%
	BN.1	VOC	2.9%	2.3-3.8%
	BA.2.75	VOC	2.6%	2.0-3.5%
	BA.5.2.6	VOC	1.8%	1.5-2.2%
	BF.11	VOC	1.1%	0.8-1.4%
	BA.2	VOC	0.8%	0.5-1.1%
	BA.2.75.2	VOC	0.6%	0.4-0.7%
	BA.4	VOC	0.0%	0.0-0.1%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.1%	0.0-0.1%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2, BN.1,XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. For all the lineages listed in the above table, their sublineages are agg..

Figure 1: CDC Nowcast data ending the Week of November 26, 2022, source: https://covid.cdc.gov/covid-data-tracker/#variant-proportions (accessed 11/26/2022)

[3] See https://www.hhs.gov/about/agencies/iea/regional-offices/index.html
[4] Source (accessed on 1/22/2022): https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-proportions.html#variant-proportions

Currently, there are no authorized point-of-care tests that can expeditiously determine the SARS-CoV-2 variant that a patient is infected with in order to guide time-sensitive treatment decisions; therefore, all therapy decisions are empiric and national and regional epidemiology are important to guide appropriate therapy choices.

The Agency recognizes that bebtelovimab retains activity against other less prevalent circulating SARS-CoV-2 variants. In addition, bebtelovimab may have activity against future circulating SARS-CoV-2 variants and, over time, the susceptibility patterns of our available countermeasures may shift. It's also important to underscore that the known and potential benefits of bebtelovimab when used to treat a patient with mild-to-moderate COVID-19 that is likely caused by a susceptible variant to this therapy, consistent with the terms and conditions of the authorization, outweigh the known and potential risks.

Moreover, the conditions to the authorization for bebtelovimab include requirements for monitoring and testing the authorized product against any global SARS-CoV-2 variant(s) of interest. Such requirements are essential to the Agency's continued understanding of bebtelovimab under this EUA.

Regulatory Conclusion and Associated Actions:

Given that a COVID-19 infection is likely to be caused by a non-susceptible SARS-CoV-2 subvariant, and consistent with the terms and conditions of the Letter of Authorization, bebtelovimab is not currently authorized for emergency use in any U.S. region at this time. FDA will also communicate publicly on the FDA website that bebtelovimab is not authorized for use in any U.S. region; and, therefore, may not be administered for treatment of COVID-19 under the EUA until further notice by the Agency.

The Agency will continue monitoring circulating variants that may impact the use of bebtelovimab and provide updates as new information becomes available.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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