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 3, 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

Rationale and Revisions to EUA Fact Sheet

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 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]

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.

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 variants. 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 variant lineages showed significant reductions in bebtelovimab neutralizing activity, presumably due to the K444T substitution encoded in the spike protein.

At this time, based on CDC's Nowcast model data as of October 29, 2022, it is estimated that BQ.1 and BQ 1.1 accounts for 14% (95% Prediction Interval [PI] 11.2-17.5%) and 13.1% (PI 9.8-17.3%) respectively, of the relative proportions of circulating SARS-CoV-2 variants circulating in the United States and in U.S. territories and jurisdictions. However, while this is a national estimate, there is variability in the prevalence of these variants across the HHS regions

[1] In implementing this LOAU, FDA will 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.

of the U.S. (e.g., HHS Region 2: 10/29/22, BQ.1: 23.5% total (95% PI 16.8-31.7%), BQ.1.1: 19% total (95% PI 12.2-28.2%); HHS Region 7: 10/29/22, BQ.1: 4.5% total (95% PI 2.1-9%), BQ.1.1: 4.4% total (95% PI 1.5-11.2%).[3]

There is significant uncertainty as to the specific prevalence of BQ.1 and BQ.1.1 in any particular state, territory, and U.S. jurisdiction at this time. Based on the current information available, there remains a likelihood that individuals may still be infected with other Omicron subvariants, for which bebtelovimab retains neutralizing activity, such as BA.5, which is the most prevalent Omicron subvariant circulating at this time in the United States and its territories and jurisdictions. FDA will continue to monitor the relative frequencies of the BQ.1. and BQ.1.1 variants to inform future regulatory decisions.

Based on the assessment of the pseudoviral data, updates to Section 12.4 and Tables 2 and 3 in the Fact Sheet for Healthcare Providers will be updated as follows.

Revisions to Section 12.4 – Fact Sheet for Healthcare Providers

Updated antiviral resistance data has been provided by Eli Lilly, and Section 12.4 of the Fact Sheet for Health Care Providers has been updated. The relevant changes are shown below.

Red font = changes by sponsor
Green font = changes by FDA

Pseudotyped VLP assessment using the full-length spike genes from different variant lineages indicate that bebtelovimab retains activity (<5-fold reduction) against the Alpha (B.1.1.7, UK origin), Beta (B.1.351, South Africa origin), Gamma (P.1, Brazil origin), Delta (B.1.617.2, India origin), Delta [+K417N] (AY.1/AY.2, India origin), Epsilon (B.1.427/B.1.429, California origin), Iota (B.1.526, New York origin), Kappa (B.1.617.1, India origin), Lambda (C.37, Peru origin), Omicron (B.1.1.529/BA.1, South Africa origin), Omicron [+R346K] (BA.1.1), Omicron BA.2, Omicron BA.2 [+L452Q] (BA.2.12.1), Omicron BA.2 [+D339H, G446S, N460K, R493Q (reversion)] (BA.2.75), Omicron BA.2 [BA.2.75+R346T+F486S] (BA.2.75.2), Omicron BA.4/BA.5, and Omicron BA.4 [+R346T] (BA.4.6) variant lineages (Table 2). The Mu (B.1.621, Colombia origin) variant showed a reduction in susceptibility to bebtelovimab of 5.3-fold. The Omicron BA.5 [+N444T, N460K] (BQ.1), and Omicron BA.5 [+R346T, N444T, N460K] (BQ.1.1) variants showed a large reduction in susceptibility to bebtelovimab of >672-fold.

Table 2: Bebtelovimab Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Spike Protein Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[b]

[3] Source (accessed on 11/1/2022): 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

B.1.351	South Africa	Beta	K417N + E484K + N501Y	No change[b]
P.1	Brazil	Gamma	K417T + E484K + N501Y	No change[b]
B.1.617.2/AY.3	India	Delta	L452R + T478K	No change[b]
AY.1/AY.2 (B.1.617.2 sublineages)	India	Delta [+K417N]	L452R + T478K + K417N	No change[b]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[b]
B.1.526[c]	USA (New York)	Iota	E484K	No change[b]
B.1.617.1	India	Kappa	L452R + E484Q	No change[b]
C.37	Peru	Lambda	L452Q + F490S	No change[b]
B.1.621	Colombia	Mu	R346K + E484K + N501Y	5.3
B.1.1.529/BA.1	South Africa	Omicron [BA.1]	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[b]
BA.1.1	South Africa	Omicron [+R346K]	BA.1 + R346K	No change[b]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[b]
BA.2.12.1	USA	Omicron [BA.2+L452Q]	BA.2 + L452Q	No change[b]
BA.2.75	India	Omicron [BA.2+D339H, G446S, N460K, R493Q (reversion)]	BA.2 + D339H, G446S, N460K, R493Q (reversion)	No change[b]
BA.2.75.2	India	Omicron [BA.2.75+R346T+F486S]	BA.2.75 + R346T + F486S	No change[b]
BA.4/BA.5	South Africa	Omicron [BA.4/BA.5]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + L452R + S477N + T478K + E484A + F486V +	No change[b]

			Q498R + N501Y + Y505H	
BA.4.6/BF.7	USA/Belgium	Omicron [BA.4+R346T]	BA.4 + R346T	No change[b]
BQ.1	Nigeria	Omicron [BA.5+K444T+N460K]	BA.5 + K444T + N460K	>672[d]
BQ.1.1	Multiple	Omicron [BA.5+R346T+K444T+N460K]	BA.5 + R346T + K444T + N460K	>672[d]

[a] Key substitutions occurring in the receptor binding domain of spike protein are listed. Pseudotyped VLP contained the full-length spike protein reflective of the consensus sequence for each of the variant lineages with the exception of BA.2.75 which is a full-length spike of BA.2.75+R346T+F486S substitutions.

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

[c] 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).

[d] Bebtelovimab is unlikely to be active against this variant.

In authentic SARS-CoV-2 assays, bebtelovimab retained activity (<5-fold reduction) against variant virus isolates from the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2/AY.3), Omicron (B.1.1.529/BA.1), Omicron [+R346K] (BA.1.1), Omicron BA.2, Omicron BA.2 [+L452Q] (BA.2.12.1), Omicron BA.2 [+D339H, G446S, N460K, R493Q (reversion)] (BA.2.75), Omicron BA.4, Omicron BA.4 [+R346T] (BA.4.6), and Omicron BA.5 lineages, as well as SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the L452R substitution present in the Epsilon (B.1.427/B.1.429) lineage or the E484K substitution present in the Iota (B.1.526) lineage (Table 3).

Table 3: Authentic[a] SARS-CoV-2 Neutralization Data for Bebtelovimab

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[b]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[c]
B.1.351	South Africa	Beta	K417N, E484K, N501Y	No change[c,d]
P.1	Brazil	Gamma	K417T, E484K, N501Y	No change[c]
B.1.617.2/AY.3	India	Delta	L452R, T478K	No change[c,d]
B.1.427/B.1.429	USA (California)	Epsilon	L452R	No change[c]
B.1.526[e]	USA (New York)	Iota	E484K	No change[c]
B.1.1.529/BA.1	South Africa	Omicron	G339D + S371L + S373P + S375F + K417N + N440K + G446S + S477N + T478K + E484A + Q493R + G496S + Q498R + N501Y + Y505H	No change[c,d]
BA.1.1	South Africa	Omicron [+R346K]	BA.1 + R346K	No change[c]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A +	No change[c,d]

			Q493R + Q498R + N501Y + Y505H	
BA.2.12.1	USA	Omicron [BA.2+L452Q]	BA.2 + L452Q	No change[c]
BA.2.75	India	Omicron [BA.2+D339H, G446S, N460K, R493Q (reversion)]	BA.2 + D339H + G446S + N460K + R493Q (reversion)	No change[c,d]
BA.4	South Africa	Omicron [BA.4]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + L452R + S477N + T478K + E484A + F486V + Q498R + N501Y + Y505H	No change[c]
BA.4.6	USA	Omicron [BA.4+R346T]	BA.4 + R346T	No change[c]
BA.5	South Africa	Omicron [BA.4/BA.5]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + L452R + S477N + T478K + E484A + F486V + Q498R + N501Y + Y505H	No change[c]

[a] The B.1.1.7, B.1.351, B.1.617.2, B.1.1.529/BA.1, and BA.2 variants were assessed using cell culture-expanded virus isolates and tested using a plaque reduction assay; the B.1.351, P.1, B.1.617.2, B.1.1.529/BA.1, BA.1.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.4.6, and BA.5 variants were assessed using cell culture-expanded isolates and tested using a microneutralization assay with a CPE-based endpoint titer to determine the $IC_{>99}$; the B.1.526/E484K, B.1.427/B.1.429/L452R, and BA.2.75 spike substitutions were assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate with E484K, L452R, or full spike of BA.2.75) and tested using a plaque reduction assay.

[b] Key substitutions occurring in receptor binding domain of spike protein which are associated with each lineage.

[c] No change: <5-fold reduction in susceptibility when compared to ancestral control isolate using the same methodology.

[d] These viral variants have been tested with two different neutralization methodologies, both yielding <5-fold reductions in susceptibility.

[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).

Revisions to Fact Sheet for Patients, Parents, and Caregivers

Previously, the Fact Sheet for Patients, Parents, and Caregivers had provided instructions for reporting side effects of bebtelovimab, either by accessing the FDA MedWatch website, or by email, fax, or telephone. The Applicant has removed the email address as they state that this is not aligned with company procedures. They argue that adverse events should be reported by fax or telephone to enable appropriate and timely review of each event.

Regulatory Conclusion:

The analysis of benefits and risks that underlie the authorization of EUA 111 remains unchanged. FDA will monitor the situation closely and provide updates as needed.

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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