



MEMORANDUM

To: Peter Stein, Director, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)
Patrizia Cavazzoni, Director, CDER
Denise Hinton, FDA Chief Scientist

From: John Farley, Director, Office of Infectious Diseases, OND, CDER
Debra Birnkrant, Director, Division of Antivirals, OND, CDER
Jeffrey Murray, Deputy Director, Division of Antivirals, OND, CDER
Wendy Carter, Clinical Team Leader, Division of Antivirals, OND, CDER
Natalie Pica, Clinical Reviewer, Division of Antivirals, OND, CDER
Jules O’Rear, Clinical Virology Team Leader, Division of Antivirals, OND, CDER
Michael Thomson, Clinical Virology Reviewer, Division of Antivirals, OND, CDER

Date: April 16, 2021

Subject: Recommendation for Revocation of EUA 090: 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

Executive Summary

On October 6, 2020, Eli Lilly and Company (Lilly) requested emergency use authorization (EUA) for bamlanivimab alone (700mg). Thereafter, on November 9, 2020, the United States (U.S.) Food and Drug Administration (FDA or The Agency) issued an Emergency Use Authorization (EUA) for the 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.¹

¹ The Agency’s Letter of Authorization (LOA) for bamlanivimab, initially issued on November 9, 2020, was subsequently revised on February 9, 2021, which was further revised on March 2, 2021. The LOA, dated March 2, 2021, is available on FDA’s website at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization-archived-information#covid19>

In issuing the EUA for bamlanivimab alone, the Agency concluded, based on the totality of scientific evidence available to FDA at the time, including data from adequate and well-controlled clinical trials, that it was reasonable to believe that bamlanivimab alone may be effective in treating COVID-19, and that the known and potential benefits of bamlanivimab when used for the treatment of COVID-19 outweighed the known and potential risks when used consistent with the terms and conditions of the authorization.² As noted in FDA's LOA to Lilly, the authorization specifically excluded the use of bamlanivimab alone in adults and pediatric patients who are hospitalized due to COVID-19, adults and pediatric patients who require oxygen therapy due to COVID-19, and adults and pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity.³

Since the initial authorization of bamlanivimab for emergency use, there has been a sustained increase in SARS-CoV-2 viral variants across the U.S. that are resistant to bamlanivimab alone. As part of the Agency's ongoing review of the circumstances and appropriateness of the EUA, we reviewed the emerging information and assessed whether, based on the totality of scientific evidence available, the criteria for issuance of the EUA continue to be met.⁴

A summary of these new data and new information includes the following:

- Vesicular stomatitis virus-based pseudovirus expressing spike protein with variant substitutions, specifically E484K and L452R, exhibit large reductions (>1,000 fold) in susceptibility to bamlanivimab alone in neutralization assays.
- The Center for Disease Control (CDC) national genomic surveillance program has reported an increasing frequency of SARS-CoV-2 variants that are expected to be resistant to bamlanivimab alone.
 - As of mid-March 2021, approximately 20% of isolates sequenced in the U.S. were reported as lineages expected to be resistant to bamlanivimab alone, increasing from approximately 5% in mid-January 2021.
 - The CDC national genomic surveillance program has published detailed data regarding variants of the B.1.427 and B.1.429 lineages, first detected in California, which harbor the L452R substitution. These variants have now been identified at frequencies exceeding 20% in eight states and frequencies exceeding 10% in two additional states.
 - There are recent reports that variants with the E484K substitution are circulating at rates exceeding 10% in the New York City metropolitan area including northern New Jersey.
- Testing technologies that enable health care providers to test individual patients for SARS-CoV-2 viral variants prior to initiation of treatment with monoclonal antibodies

² Section 564(c) of the Federal Food, Drug and Cosmetic Act (FD&C Act) sets forth the criteria that must be met for the Agency to issue an EUA.

³ Supra note 1.

⁴ See section 564(g) of the FD&C Act.

are not available⁵ and frequencies are changing rapidly. Therefore, empiric treatment with monoclonal antibody therapies that are expected to retain activity broadly across the U.S. are needed to reduce the likelihood of treatment failure.⁶

- On April 8, 2021, the National Institutes of Health updated its treatment guidelines for COVID-19 recommending against the use of bamlanivimab alone.^{7,8}

Given the above, we have concluded that the known and potential benefits of bamlanivimab alone no longer outweigh the known and potential risks for the product.⁹ Therefore, we believe that the criteria¹⁰ for issuance of an authorization are no longer met and we recommend revocation of EUA 090.^{11,12}

Authorization of EUA 090

Bamlanivimab is a recombinant neutralizing human IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. On November 9, 2020, FDA concluded that, based on the totality of scientific evidence available at the time, including the topline data from the planned interim analysis of Trial J2W-MC-PYAB, also called BLAZE-1, it was reasonable to believe that bamlanivimab alone may be effective for the treatment of mild to moderate COVID-19 for certain adult and pediatric patients, and that when used consistent with the terms and conditions of the authorization, the known and potential benefits of bamlanivimab alone outweighed the known and potential risks of the product.¹³ FDA's determination was based, in part, on the reduction of hospitalization or Emergency Room visit events seen in the treatment groups relative to placebo (pooled bamlanivimab 5/309 (2%) vs placebo (6%) p=0.02

⁵ As noted in the authorized labeling for the monoclonal antibody therapies, such as bamlanivimab and etesevimab administered together, as well as REGEN-COV, initiation of treatment should occur as soon as possible after positive results of direct SARS-CoV-2 viral testing.

⁶ Alternative monoclonal antibody therapies that are currently authorized for emergency use, such as bamlanivimab and etesevimab administered together, as well as REGEN-COV, remain appropriate to treat patients with COVID-19 when used in accordance with the authorized labeling based on information available at this time.

⁷ <https://www.covid19treatmentguidelines.nih.gov/statement-on-anti-sars-cov-2-monoclonal-antibodies-eua/>

⁸ In addition, we note that On March 24, 2021, the U.S. Government, in coordination with Eli Lilly and Company, ceased distribution of bamlanivimab alone. The Office of the Assistant Secretary for Preparedness and Response and FDA issued a joint statement on the distribution of bamlanivimab, which is located at:

<https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx>

⁹ The epidemiology of variants, which vary from country to country, are central to the Agency's assessment as to whether the known and potential benefits of bamlanivimab alone, when used for the treatment of COVID-19 as previously authorized, outweigh the known and potential risks of the product.

¹⁰ See Section 564(c) of the FD&C Act.

¹¹ See Section 564(g)(2) of the FD&C Act.

¹² On April 15, 2021, Lilly submitted a request to FDA to revoke the EUA for bamlanivimab alone. At the time of Lilly's request, the Agency, based on the totality of scientific evidence available, had determined that the revocation of EUA 090 was appropriate pursuant to section 564(g)(2)(B) of the FD&C Act.

¹³ Under section 564(c) of the FD&C Act, FDA must also determine that there is no adequate, approved and available alternative to the authorized product. At the time EUA 090 was issued, FDA had already approved Veklury (remdesivir) and authorized other EUAs for COVID-19 treatments. For example, VEKLURY (remdesivir) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor approved for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Veklury was initially authorized for emergency use on May 1, 2020, and was subsequently approved on October 22, 2020 under NDA 214787.

[95% CI: 1%, 9%]). In addition, the median time to symptom improvement was shorter in patients who received bamlanivimab relative to placebo.¹⁴

At the time EUA 090 was authorized, Lilly was prioritizing the development of a second anti-spike monoclonal antibody, etesevimab, that if authorized for emergency use, would be administered together with bamlanivimab. Generally, the administration of two monoclonal antibodies together may be less likely to be associated with the risk of treatment failure when used to treat a patient infected with a circulating viral variant resistant to bamlanivimab alone, or viral variants emerging during treatment resistant to bamlanivimab alone. On February 9, 2021, bamlanivimab and etesevimab administered together was authorized for emergency 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, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.^{15, 16}

Review of New Information Relevant to Assessing Whether the Known and Potential Benefits of Bamlanivimab Alone for Treating COVID-19 Outweigh the Known and Potential Risks

Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitution with Bamlanivimab Alone

Given the emergence of viral variants of SARS-CoV-2 known to be circulating in the U.S., the Division of Antivirals¹⁷ requested that Lilly conduct cell culture neutralization studies to assess the activity of bamlanivimab alone against these variants, and/or amino acid substitutions found in these variants.¹⁸ The Sponsor provided pseudovirus data for spike protein substitutions found in lineages B.1.1.7 (first detected in UK), B.1.351 (first detected in South Africa), P.1 (first detected in Brazil), B.1.427/B.1.429 (first detected in California), and B.1.526 (first detected in New York) (Table 1).¹⁹

¹⁴ See FDA Decision Memo for EUA 090, dated November 9, 2020.

¹⁵ See: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs> for the Letter of Authorization and Health Care Provider Fact Sheet for EUA 094.

¹⁶ On November 21, 2020, FDA also authorized REGEN-COV (casirivimab and imdevimab) for emergency 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 SAR-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. See: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs> for the Letter of Authorization and Health Care Provider Fact Sheet for EUA 091.

¹⁷ The Division of Antivirals is within the Office of Infectious Diseases in the Center for Drug Evaluation and Research's Office of New Drugs.

¹⁸ See the administrative records for IND 150440 and EUA 90.

¹⁹ These findings are similar to other published studies. See for example: Wang, P. et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. *Nature* <https://doi.org/10.1038/s41586-021-03398-2> (2021).

Table 1: 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 (first detected UK)	N501Y	no change ^b
B.1.351 (first detected South Africa)	E484K	>2,360 ^c
P.1 (first detected Brazil)	E484K	>2,360 ^c
B.1.427/B.1.429 (first detected California)	L452R	>1,020 ^c
B.1.526 (first detected New York) ^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)

While it is not known how pseudovirus data correlate with clinical outcomes, reduction in susceptibility of >1,000-fold indicates that there will likely be no activity of bamlanivimab alone against variants with E484K and L452R substitutions. These data (Table 1), along with a recommendation for prescribing healthcare providers to consider the prevalence of variants resistant to bamlanivimab alone in their area, where data are available, when considering available treatment options, were added to the Fact Sheet for Health Care Providers on March 18, 2021.²⁰

Epidemiological Data Regarding SARS-CoV-2 Variants

The Centers for Disease Control, along with state and other public health agencies and researchers, have been monitoring new and emerging variants in order to inform public health actions.²¹ The proportion of variants resistant to bamlanivimab alone has been increasing since early January 2021. For example, the proportion of resistant isolates was approximately 5% for the week ending January 16, 2021. As of mid-March 2021, approximately 20 percent of sequenced variants nationally were expected to be resistant to bamlanivimab alone.²² See Figure 1. There are data gaps that exist as these surveillance efforts intensify with information currently inadequate to estimate frequency for some states. For example, state-level data are currently available for 39 states. Thus, these proportions may be underestimates.

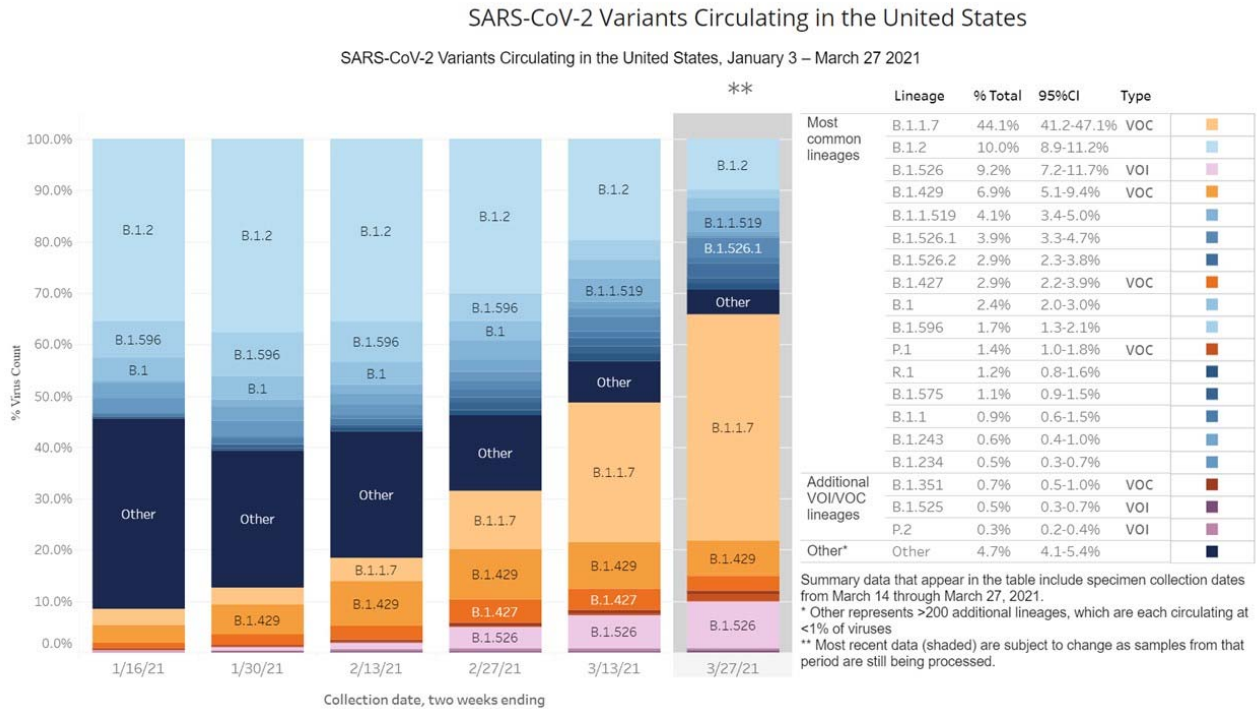
²⁰ See: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization-archived-information#covid19> for the Health Care Provider Fact Sheet.

²¹ Available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html> Accessed April 15, 2021.

²² The majority of isolates of the B.1.526 lineage (first detected New York) harbor the E484K substitution which results in bamlanivimab resistance. All of the isolates of the B.1.427 and B.1.429 lineage (first detected California) harbor the L452R substitution which results in bamlanivimab resistance.

Figure 1: Increasing Frequency of SARS-CoV-2 Variants Circulating in the United States, January 2-March 27, 2021,

Source: CDC, Variant Proportions in the U.S., Available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html> Accessed April 15, 2021.



With respect to the variants B.1.427 and B.1.429 (first detected California) harboring the L452R substitution leading to resistance to bamlanivimab alone, CDC reports that more than 20% of the sequenced isolates from the States of Arizona, California, Colorado, Nevada, New Mexico, Oregon, Utah, and Washington and more than 10% of the sequenced isolates from the States of Illinois and Minnesota were of the B.1.427 or B.1.429 lineage.

The majority of isolates of the B.1.526 lineage (first detected New York) harbor the E484K substitution, which also results in bamlanivimab resistance. Manuscripts publicly available and currently under peer review have focused on the E484K substitution rather than lineage and report that this substitution increased to greater than 10% of isolates sequenced in the New York City metropolitan area (New York City and Northern New Jersey) in February 2021.^{23,24} The E484K substitution has been identified in the U.S. in variants of lineages other than B.1.526 (first detected New York), B.1.351 (first detected South Africa), and P.1 (first detected Brazil).²⁵ Substitution specific rather than lineage specific surveillance data are very limited in the U.S. at this time. Thus, the frequency of the E484K substitution may be under-reported.

²³ Annavajhala, MK, et al. (2021). A Novel SARS-CoV-2 Variant of Concern, B.1.526, Identified in New York. *medRxiv*, 2021. doi:10.1101/2021.02.23.21252259

²⁴ Zhao, Y et al. (2021) A Novel Diagnostic Test to Screen SARS-CoV-2 Variants Containing E484K and N501Y Mutations. *medRxiv*, 2021. doi:10.1101/2021.03.26.21253712

²⁵ Lesho, E, et al. (2021). Emergence of the E484K Mutation in SARS-CoV-2 Lineage B.1.1.220 in Upstate New York. *medRxiv*, 2021. doi:10.1101/2021.03.11.21253231

Inadequate Testing Technologies/Risk of Treatment Failure/Empiric Treatment

Authorized labeling for bamlanivimab alone advises healthcare providers to initiate treatment as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of onset of symptoms. Testing technologies are not available for healthcare providers to obtain information prior to initiating treatment to ascertain whether a patient who has tested positive for SARS-CoV-2 is infected with a particular viral variant that is resistant to bamlanivimab alone. As such, there is a significant risk of treatment failure should bamlanivimab be administered alone to a patient who is infected with a resistant SARS-CoV-2 variant. Empiric treatment using other authorized monoclonal antibody therapies that are expected to retain activity against circulating viral variants is essential to achieving public health goals.²⁶

U.S. National Institutes of Health Treatment Guidelines

On April 8, 2021, the National Institutes of Health updated its treatment guidelines for COVID-19 recommending against the use of bamlanivimab alone.²⁷ The Panel recommended using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria: bamlanivimab 700 mg plus etesevimab 1,400 mg; *or* casirivimab 1,200 mg plus imdevimab 1,200 mg (also referred to as REGEN-COV). Because clinical outcome data are limited and there are concerns regarding decreased susceptibility of variants, the Panel recommended against the use of bamlanivimab monotherapy.

Additional Information

On March 24, 2021, the U.S. Government, in coordination with Eli Lilly and Company, stopped the distribution of bamlanivimab alone throughout the U.S. Stakeholders may order etesevimab alone to pair with existing supply of bamlanivimab that may be on hand, or the two other authorized monoclonal antibodies, bamlanivimab and etesevimab administered together or REGEN-COV. At this time, bamlanivimab and etesevimab administered together, as well as REGEN-COV are available in adequate supply per the Department of Health and Human Services Assistant Secretary for Preparedness and Response.

Conclusion

Since FDA initially authorized bamlanivimab alone for emergency use on November 9, 2020, new data and information have become available regarding whether the known and potential benefits of bamlanivimab alone outweigh the known and potential risks associated with its authorized use in the context of newly emergent viral variants. We have reviewed this

²⁶ Alternative monoclonal antibody therapies that are currently authorized for emergency use, such as bamlanivimab and etesevimab administered together, as well as REGEN-COV, are expected to retain activity against most circulating viral variants and are currently available in sufficient supply to meet the emergency need.

²⁷ <https://www.covid19treatmentguidelines.nih.gov/statement-on-anti-sars-cov-2-monoclonal-antibodies-eua/>

information as part of our ongoing assessment of whether continued authorization of EUA 090 remains appropriate.

Based on our review, we have determined the following:

- Nonclinical data demonstrate that pseudoviruses that harbor E484K and L452R spike substitutions have reduced susceptibility to bamlanivimab.
- Surveillance data demonstrate that as of mid-March 2021, approximately 20% of isolates sequenced in the U.S. overall were expected to be resistant to bamlanivimab alone. This proportion is higher than 20% in at least 8 states.
- It is not feasible for clinicians to test individuals for SARS-CoV-2 viral variants prior to treatment with monoclonal antibodies. Empiric treatment with monoclonal antibodies that are expected to retain activity against circulating viral variants across the U.S. is necessary to avoid the risk of treatment failure.
- The National Institutes of Health recently updated its treatment guidelines for COVID-19 to recommend against the use of bamlanivimab monotherapy.

In summary, the frequency of circulating variants resistant to bamlanivimab alone has resulted in a significant risk for treatment failure, should bamlanivimab be administered alone, and as such, empiric treatment using other authorized monoclonal antibody therapies that are expected to retain activity against circulating viral variants is essential to achieving public health goals. The recommendation for prescribing healthcare providers to consider the prevalence of variants resistant to bamlanivimab alone in their area, where data are available, when considering available treatment options, added to the Fact Sheet for Health Care Providers on March 18, 2021, is no longer adequate to ensure that the known and potential benefits outweigh the known and potential risks. Therefore, based on the totality of scientific evidence available, it is no longer reasonable to believe that the known and potential benefits of bamlanivimab alone in treating COVID-19 for the uses specified in EUA 090 outweigh the known and potential risks associated with its authorized use.

Recommendation

Based on the above, we believe that the criteria for Emergency Use Authorization as outlined in Section 564(c)(2) of the FD&C Act are no longer met and recommend the revocation of EUA 090.

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/

LINDA C AKUNNE
04/16/2021 02:22:18 PM

MICHAEL THOMSON
04/16/2021 02:28:00 PM

NATALIE M PICA
04/16/2021 02:31:48 PM

WENDY W CARTER
04/16/2021 02:45:20 PM

JEFFREY S MURRAY
04/16/2021 02:47:35 PM

JOHN J FARLEY
04/16/2021 02:52:16 PM