March 2, 2021

Eli Lilly and Company
Attention: Christine Phillips, PhD, RAC
Advisor Global Regulatory Affairs - US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

RE: Emergency Use Authorization 090

Dear Ms. Phillips:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On November 9, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of bamlanivimab 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. Bamlanivimab is a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. It is an investigational drug and is not currently approved for any indication.

On February 9. 2021, FDA reissued the November 9, 2020 letter.[3]

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] FDA revised the condition on requesting changes to this authorization, including changes to the authorized Fact Sheets. New conditions were also incorporated relating to the development of instructional or educational materials, as well as certain mandatory reporting requirements for healthcare facilities and providers. In addition to certain editorial and/or clarifying revisions, the Fact Sheet for Healthcare Providers was revised to include information on the new mandatory reporting requirements on therapeutics information and utilization data for healthcare facilities and providers.

Subsequently, on March 2, 2021, FDA reissued the February 9, 2021 letter.[4]

On March 2, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the February 9, 2021 letter in its entirety to include technical revisions to the description of the authorized product.

Based on review of the topline data from the planned interim analysis of Trial J2W-MC-PYAB, also called BLAZE-1 (NCT04427501), an ongoing randomized, double-blind, placebo-controlled, Phase 2 dose finding trial of bamlanivimab monotherapy in outpatients with mild to moderate COVID-19, it is reasonable to believe that bamlanivimab may be effective 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, and that, when used under the conditions described in this authorization, the known and potential benefits of bamlanivimab outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of bamlanivimab for the treatment of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of bamlanivimab for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that bamlanivimab may be effective in treating 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, and that, when used under the conditions described in this authorization, the known and potential benefits of bamlanivimab outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of bamlanivimab 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

[4] FDA further revised the condition on instructional and educational materials. New conditions were also incorporated on the establishment of a process for monitoring genomic databases for the emergence of global viral variants of SARS-CoV-2 and the assessment, if requested by FDA, of the activity of the authorized bamlanivimab against any global SARS-CoV-2 variant(s) of interest.

direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.[5]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized bamlanivimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab to authorized distributors[6], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- The bamlanivimab covered by this authorization will be used only by healthcare providers to treat 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;

- Bamlanivimab is not authorized for use in the following patient populations[7]:

    - Adults or pediatric patients who are hospitalized due to COVID-19, or
    - Adults or pediatric patients who require oxygen therapy due to COVID-19, or
    - Adults or 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.

- Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- The use of bamlanivimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description

[5] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[6] "Authorized Distributor(s)" are identified by Lilly as an entity or entities allowed to distribute authorized bamlanivimab.
[7] Benefit of treatment with bamlanivimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Bamlanivimab is a neutralizing IgG1 monoclonal antibody that binds to the receptor binding domain of the spike protein of SARS-CoV-2. Bamlanivimab, injection, 700 mg/20 mL, is a sterile, preservative-free aqueous solution that is to be diluted by withdrawing 20 mL of bamlanivimab from a single 20 mL vial, which is then transferred to a 0.9% Sodium Chloride Injection infusion bag. The authorized bamlanivimab includes a vial label and/or carton labeling that is clearly marked for "emergency use authorization".

Bamlanivimab, injection, 700 mg/20 mL, vials should be stored in unopened vials under refrigerated temperature at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Diluted bamlanivimab infusion solution can be stored for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time.

Bamlanivimab is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Lilly's website at www.bamlanivimab.com:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Bamlanivimab

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of Bamlanivimab for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of bamlanivimab, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that bamlanivimab may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that bamlanivimab (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), bamlanivimab is authorized to treat 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, as described in the Scope of Authorization

(Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Eli Lilly and Company (Lilly) and Authorized Distributors

A. Lilly and authorized distributor(s) will ensure that the authorized bamlanivimab is distributed, as directed by the U.S. government, and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Lilly and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Lilly and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized bamlanivimab. Lilly will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Lilly may request changes to this authorization, including to the authorized Fact Sheets for bamlanivimab. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[8]

E. Lilly may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the emergency use of bamlanivimab as described in this letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet the public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized

[8] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

labeling, the Agency will require Lilly to cease distribution of such instructional or educational materials.

F. Lilly will report to FDA serious adverse events and all medication errors associated with the use of the authorized bamlanivimab that are reported to Lilly using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options should state: "bamlanivimab use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

H. Lilly will retain an independent third party (i.e., not affiliated with Lilly) to conduct a review of the batch records and any underlying data and associated discrepancies of bamlanivimab drug substance manufactured at Lilly Branchburg, NJ.

- For all batches manufactured prior to the effective date of this authorization, these batches can be released while review is ongoing.
- For all batches manufactured after the effective date of this authorization, the third party review can be performed concurrent to Lilly's batch release process.

If the independent review finds, prior to release, a discrepancy with significant potential to affect critical quality attributes, the product must not be released unless and until the issue is satisfactorily resolved. Any discrepancies found by the independent review, whether prior to or after release, must be reported to the Agency in a summary report, submitted every 14 calendar days, and include Lilly's corrective and preventive action plans for each discrepancy, including whether market action is required. The plans must include an appropriate evaluation of each discrepancy's potential impact on any released drug substance and associated drug product.

I. Lilly will retain an independent third-party (i.e., not affiliated with Lilly) to conduct laboratory release testing of bamlanivimab drug substance manufactured at Lilly, Branchburg (excluding bioburden and endotoxin testing). Any discrepancies found by the independent laboratory must be reported to the Agency in a summary report, submitted every 14 calendar days, and include Lilly's corrective and preventive action plans for each

discrepancy. The plans must include an appropriate evaluation of each discrepancy's potential impact on any released drug substance and associated drug product.

J. Lilly will submit information to the Agency within three working days of receipt of any information concerning any batch of bamlanivimab (whether the batch is distributed or not), as follows: (1) information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; and (2) information concerning any microbiological contamination, or any significant chemical, physical, or other change in deterioration in the drug product, or any failure of one or more batches of the drug product to meet the established specifications. Lilly will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Lilly must recall them.

K. Lilly will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product without notification to and concurrence by the Agency as described under condition D.

L. Lilly will manufacture and test bamlanivimab per the process and methods, including in-process sampling and testing and finishing product testing (release and stability) to meet all specifications as detailed in Lilly's EUA request.

M. Lilly will list bamlanivimab with a unique product NDC under the marketing category of Unapproved Drug- Other. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

N. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of the authorized bamlanivimab (i.e., lot numbers, quantity, receiving site, receipt date).

O. Lilly and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

P. Lilly will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Lilly's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Lilly will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

Q. FDA may require Lilly to assess the activity of the authorized bamlanivimab against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Lilly will perform the required assessment in a manner and timeframe agreed upon by Lilly and the Agency. Lilly will submit to FDA a preliminary summary

report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Lilly will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

Healthcare Facilities to Whom the Authorized Bamlanivimab Is Distributed and Healthcare Providers Administering the Authorized Bamlanivimab

R. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of bamlanivimab.

S. Healthcare facilities and healthcare providers receiving bamlanivimab will track serious adverse events that are considered to be potentially attributable to bamlanivimab use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "bamlanivimab use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

T. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the product is administered consistent with the terms of this letter.

U. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized bamlanivimab (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

V. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Lilly and/or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.

W. Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Conditions Related to Printed Matter, Advertising and Promotion

X. All descriptive printed matter, as well as advertising and promotional material, relating to the use of the bamlanivimab under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

Y. No descriptive printed matter, as well as advertising or promotional material, relating to the use of bamlanivimab may represent or suggest that such products are safe or effective when used 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.

Z. All descriptive printed matter, as well as advertising and promotional material, relating to the use of the bamlanivimab clearly and conspicuously shall state that:

- the bamlanivimab has not been approved, but has been authorized for emergency use by FDA, to treat 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.

- the bamlanivimab is authorized 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 only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the bamlanivimab under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

February 25, 2021

Eli Lilly and Company
Attention: Christine Phillips, PhD, RAC
Advisor Global Regulatory Affairs - US
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

RE: Emergency Use Authorization 094

Dear Ms. Phillips:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On February 9, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of bamlanivimab and etesevimab administered together 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. Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2. They are both investigational drugs and are not currently approved for any indication.

On February 25, 2021, having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the February 9, 2021 letter in its entirety with revisions incorporated to the condition on instructional and educational materials. New conditions have also been incorporated on the establishment of a process for monitoring genomic databases for the emergence of global viral variants of SARS-CoV-2 and

[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.
[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

the assessment, if requested by FDA, of the activity of the authorized bamlanivimab and etesevimab against any global SARS-CoV-2 variant(s) of interest.

Based on the review of the data from the Phase 2/3 BLAZE-1 trial (NCT04427501), an ongoing randomized, double-blind, placebo-controlled clinical trial, and the Phase 2 BLAZE-4 trial (NCT04634409), an ongoing randomized, double-blind, placebo-controlled clinical trial, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective 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, and that, when used under the conditions described in this authorization, the known and potential benefits of bamlanivimab and etesevimab administered together outweigh the known and potential risks of such products.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of bamlanivimab for treatment of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of bamlanivimab and etesevimab for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective in treating 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, and that, when administered as described in the Scope of Authorization (Section II) and used under the conditions described in this authorization, the known and potential benefits of bamlanivimab and etesevimab outweigh the known and potential risks of such product; and

3. There is no adequate, approved, and available alternative to the emergency use of bamlanivimab and etesevimab as described in the Scope of Authorization (Section II) 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.[3]

[3] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized bamlanivimab and etesevimab will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Lilly will supply bamlanivimab and etesevimab to authorized distributors[4], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- The bamlanivimab and etesevimab covered by this authorization will be administered together only by healthcare providers to treat 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;

- Etesevimab may only be administered together with bamlanivimab[5];

- Bamlanivimab and etesevimab are not authorized for use in the following patient populations[6]:

    - Adults or pediatric patients who are hospitalized due to COVID-19, or
    - Adults or pediatric patients who require oxygen therapy due to COVID-19, or
    - Adults or 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.

- Bamlanivimab and etesevimab may only be administered together in settings in which health care providers have immediate access to medications to treat a severe

[4] "Authorized Distributor(s)" are identified by Lilly as an entity or entities allowed to distribute authorized bamlanivimab.

[5] At the time of the issuance of this EUA, bamlanivimab, a monoclonal antibody therapy, is authorized under a separate EUA as a monotherapy 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. (For a listing of FDA EUAs, see FDA's website at: Emergency Use Authorization | FDA). Etesevimab, alone, has not been evaluated as a treatment for patients with COVID-19. Etesevimab may only be administered together with bamlanivimab consistent with the terms and conditions of this authorization.

[6] Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

- The use of bamlanivimab and etesevimab covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description

Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2. Bamlanivimab injection, 700 mg/20 mL, and etesevimab, 700 mg/20 mL, are sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solutions to be diluted prior to infusion. One vial of bamlanivimab (20 mL) and two vials of etesevimab (40 mL) are to be added to a prefilled 0.9% sodium chloride infusion bag as described in the healthcare provider fact sheet. The authorized bamlanivimab includes a vial label and/or carton labeling that is clearly marked "For use under Emergency Use Authorization (EUA)". The authorized etesevimab includes a vial label and/or carton labeling that is clearly marked "For use under Emergency Use Authorization (EUA)" and "MUST ADMINISTER WITH BAMLANIVIMAB."

Bamlanivimab, injection, 700 mg/20 mL, and etesevimab, injection, 700mg/20 mL vials should be stored in unopened vials under refrigerated temperature at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Diluted bamlanivimab and etesevimab infusion solution can be stored for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time.

Bamlanivimab and etesevimab are authorized for emergency use as described in the Scope of Authorization (Section II) with the following product-specific information required to be made available to healthcare providers and patients, parents, and caregivers, respectively, through Lilly's website at www.BAMandETE.com:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of bamlanivimab and etesevimab when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that bamlanivimab and etesevimab may

be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that bamlanivimab and etesevimab (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), bamlanivimab and etesevimab administered together are authorized to treat mild to moderate COVID-19 illness 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 illness and/or hospitalization as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Eli Lilly and Company (Lilly) and Authorized Distributors

A. Lilly and authorized distributor(s) will ensure that the authorized bamlanivimab and etesevimab are distributed, as directed by the U.S. government, and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Lilly and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Lilly and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized bamlanivimab and etesevimab. Lilly will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Lilly may request changes to this authorization, including to the authorized Fact Sheets for bamlanivimab and etesevimab. Any request for changes to this EUA must be submitted to

the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[7]

E. Lilly may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of bamlanivimab and etesevimab as described in this letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling of bamlanivimab and etesevimab are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized labeling of bamlanivimab and etesevimab, the Agency will require Lilly to cease distribution of such instructional or educational materials.

F. Lilly will report to FDA serious adverse events and all medication errors associated with the use of the authorized bamlanivimab and etesevimab that are reported to Lilly using either of the following options.

   Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

   Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

   Submitted reports under both options should state: "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

H. Lilly will retain an independent third party (i.e., not affiliated with Lilly) to conduct a review of the batch records and any underlying data and associated discrepancies of bamlanivimab drug substance manufactured at Lilly Branchburg, NJ.

[7] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

- For all batches manufactured prior to the effective date of this authorization, these batches can be released while review is ongoing.
- For all batches manufactured after the effective date of this authorization, the third party review can be performed concurrent to Lilly's batch release process.

If the independent review finds, prior to release, a discrepancy with significant potential to affect critical quality attributes, the product must not be released unless and until the issue is satisfactorily resolved. Any discrepancies found by the independent review, whether prior to or after release, must be reported to the Agency in a summary report, submitted every 14 calendar days, and include Lilly's corrective and preventive action plans for each discrepancy, including whether market action is required. The plans must include an appropriate evaluation of each discrepancy's potential impact on any released drug substance and associated drug product.

I. Lilly will retain an independent third-party (i.e., not affiliated with Lilly) to conduct laboratory release testing of bamlanivimab drug substance manufactured at Lilly, Branchburg (excluding bioburden and endotoxin testing). Any discrepancies found by the independent laboratory must be reported to the Agency in a summary report, submitted every 14 calendar days, and include Lilly's corrective and preventive action plans for each discrepancy. The plans must include an appropriate evaluation of each discrepancy's potential impact on any released drug substance and associated drug product.

J. Lilly will submit information to the Agency within three working days of receipt of any information concerning any batch of bamlanivimab or etesevimab (whether the batch is distributed or not), as follows: (1) information concerning any incident that causes the product or its labeling to be mistaken for, or applied to, another article; and (2) information concerning any microbiological contamination, or any significant chemical, physical, or other change in deterioration in the product, or any failure of one or more batches of the product to meet the established specifications. Lilly will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Lilly must recall them.

K. Lilly will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product without notification to and concurrence by the Agency as described under condition D.

L. Lilly will manufacture and test bamlanivimab and etesevimab per the process and methods, including in-process sampling and testing and finishing product testing (release and stability) to meet all specifications as detailed in Lilly's EUA request.

M. Lilly will individually list bamlanivimab and etesevimab with a unique product NDC under the marketing category of Unapproved Drug- Other. Further, each listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

N. Through a process of inventory control, Lilly and authorized distributor(s) will maintain records regarding distribution of the authorized bamlanivimab and etesevimab (i.e., lot numbers, quantity, receiving site, receipt date).

O. Lilly and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

P. Lilly will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Lilly's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Lilly will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

Q. FDA may require Lilly to assess the activity of the authorized bamlanivimab and etesevimab against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Lilly will perform the required assessment in a manner and timeframe agreed upon by Lilly and the Agency. Lilly will submit to FDA a preliminary summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Lilly will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

Healthcare Facilities to Whom the Authorized Bamlanivimab and Etesevimab Are Distributed and Healthcare Providers Administering the Authorized Bamlanivimab and Etesevimab

R. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of bamlanivimab and etesevimab as described in the Scope of Authorization (Section II) under this EUA.

S. Healthcare facilities and healthcare providers receiving bamlanivimab and etesevimab will track serious adverse events that are considered to be potentially attributable to the use of bamlanivimab and etesevimab under this authorization and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)" at the beginning of the question "Describe Event" for further analysis.

T. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the products are administered consistent with the terms of this letter.

U. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized bamlanivimab and etesevimab (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

V. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Lilly and/or FDA. Such records will be made available to Lilly, HHS, and FDA for inspection upon request.

W. Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Conditions Related to Printed Matter, Advertising and Promotion

X. All descriptive printed matter, as well as advertising and promotional material, relating to the use of the bamlanivimab and etesevimab under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

Y. No descriptive printed matter, as well as advertising or promotional material, relating to the use of bamlanivimab and etesevimab under this authorization may represent or suggest that such products are safe or effective when used 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.

Z. All descriptive printed matter, as well as advertising and promotional material, relating to the use of the bamlanivimab and etesevimab under this authorization clearly and conspicuously shall state that:

- Bamlanivimab and etesevimab have not been approved, but have been authorized for emergency use by FDA to be administered together 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.

- Bamlanivimab and etesevimab s are authorized to be administered together 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 only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the

bamlanivimab under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

--/S/--

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

February 25, 2021

Regeneron Pharmaceuticals, Inc.
Attention: Yunji Kim, PharmD
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

RE: Emergency Use Authorization 091

Dear Dr. Kim:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On November 21, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of REGEN-COV (casirivimab and imdevimab, administered together)[3] 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. Casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. They are investigational drugs and are not approved for any indication.

On February 3, 2021, FDA reissued the November 21, 2020 letter.[4]

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] The November 21, 2020 EUA referred to the authorized product as "casirivimab and imdevimab, administered together". Regeneron subsequently requested, and FDA concurred, that the authorized labeling be revised to add references to authorized products' trade name, "REGEN-COV".

[4] FDA revised the condition on requesting changes to this authorization, including changes to the authorized Fact Sheets. New conditions were also incorporated relating to the development of instructional or educational materials, as well as certain mandatory reporting requirements for healthcare facilities and providers. In addition to certain

On February 25, 2021, again having concluded that revising this EUA is appropriate to protect the public health or safety under section 564(g)(2) of the Act, FDA is reissuing the February 3, 2021 letter in its entirety with revisions incorporated to the condition on instructional and educational materials. New conditions have also been incorporated on the establishment of a process for monitoring genomic databases for the emergence of global viral variants of SARS-CoV-2 and the assessment, if requested by FDA, of the activity of the authorized REGEN-COV against any global SARS-CoV-2 variant(s) of interest.

Based on review of the analysis of phase 1 and 2 data from the ongoing trial R10933-10987-COV-2067 (NCT04425629), a phase 1/2/3, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of casirivimab and imdevimab 2400 mg IV or casirivimab and imdevimab 8000 mg IV or placebo in outpatients (non-hospitalized) with SARS-CoV-2 infection, it is reasonable to believe that REGEN-COV may be effective 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, and that, when used under the conditions described in this authorization, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such product.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of REGEN-COV for treatment of COVID-19, as described in the Scope of Authorization section of this letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of REGEN-COV for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that REGEN-COV may be effective in treating 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, and that, when used under the conditions described in this authorization, the known and potential benefits of REGEN-COV outweigh the known and potential risks of such products; and

editorial and/or clarifying revisions, the Fact Sheet for Healthcare Providers was revised to include information on the new mandatory reporting requirements on therapeutics information and utilization data for healthcare facilities and providers. Updated safety information and details on possible side effects were also incorporated into the authorized Fact Sheets.

3. There is no adequate, approved, and available alternative to the emergency use of REGEN-COV 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.[5]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- Distribution of the authorized REGEN-COV will be controlled by the United States (U.S.) Government for use consistent with the terms and conditions of this EUA. Regeneron will supply REGEN-COV to authorized distributor(s)[6], who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities as needed;

- REGEN-COV will be used only by healthcare providers to treat 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;

- The monoclonal antibodies that comprise REGEN-COV, casirivimab and imdevimab, may only be administered together;

- REGEN-COV is not authorized for use in the following patient populations[7]:
    - Adults or pediatric patients who are hospitalized due to COVID-19, or
    - Adults or pediatric patients who require oxygen therapy due to COVID-19, or
    - Adults or 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.

- REGEN-COV may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

[5] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[6] "Authorized Distributor(s)" are identified by Regeneron as an entity or entities allowed to distribute authorized REGEN-COV.
[7] Benefit of treatment with REGEN-COV has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

- The use of REGEN-COV covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

Product Description

REGEN-COV is available in dose pack bags that will include a sufficient number of vials of casirivimab and imdevimab to prepare one treatment dose.[8] Casirivimab and imdevimab are each supplied in individual single use vials. Individual vials and carton container labeling for casirivimab and imdevimab included in dose pack bags are clearly marked "For Use under Emergency Use Authorization." Casirivimab and imdevimab are recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2.

Casirivimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion. Imdevimab is available as 300 mg/2.5 mL (120 mg/mL) or 1332 mg/11.1 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to infusion.

The dose pack bags containing unopened vials of casirivimab injection and imdevimab injection should be stored under refrigerated temperature at 2°C to 8°C (36°F to 46°F). The vials should be kept in the individual original cartons to protect from light. Diluted casirivimab and imdevimab infusion solution can be stored in the refrigerator between 2°C to 8°C (36°F to 46°F) for no more than 36 hours or at room temperature up to 25°C (77°F) for no more than 4 hours.

REGEN-COV is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients/caregivers, respectively, through Regeneron's website at www.REGENCOV.com:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of casirivimab and imdevimab

- Fact Sheet for Patients, Parents and Caregivers: Emergency Use Authorization (EUA) of casirivimab and imdevimab for Coronavirus Disease 2019 (COVID-19)

- Information Sheet ("Fact Sheet Directions")

[8] Individual vials of casirivimab and imdevimab distributed in interstate commerce prior to the reissuance of this letter remain authorized for emergency use. FDA is not requiring that such product be repackaged given the public health need for the product. The use of the individual vials of casirivimab and imdevimab must be consistent with the terms and conditions of this authorization. Individual vial labels for casirivimab and imdevimab and carton labeling may be clearly marked with either "Caution: New Drug - Limited by Federal (or United States) law to investigational use" or with "For use under Emergency Use Authorization (EUA)". Some vial labels and carton labeling of casirivimab and imdevimab may be instead labeled with the Investigational New Drug (IND) clinical trial code name as "REGN10933" and "REGN10987", respectively.

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of REGEN-COV, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh the known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that REGEN-COV may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that REGEN-COV (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), REGEN-COV is authorized to treat mild to moderate COVID-19 illness 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 progressing to severe COVID-19 illness and/or hospitalization as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Regeneron and Company (Regeneron) and Authorized Distributors

A. Regeneron and authorized distributor(s) will ensure that the authorized REGEN-COV is distributed as directed by the U.S. government, and the authorized labeling (i.e., Fact Sheets) will be made available to healthcare facilities and/or healthcare providers consistent with the terms of this letter.

B. Regeneron and authorized distributor(s) will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers.

C. Regeneron and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized REGEN-COV. Regeneron will provide to all relevant stakeholders a copy of this letter of authorization and communicate any

subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Regeneron may request changes to this authorization, including to the authorized Fact Sheets for REGEN-COV. Any request for changes to this EUA must be submitted to the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research. Such changes require appropriate authorization prior to implementation.[9]

E. Regeneron may develop and disseminate instructional and educational materials (e.g., materials providing information on product administration and/or patient monitoring) that are consistent with the authorized emergency use of REGEN-COV as described in this letter of authorization and authorized labeling, without FDA's review and concurrence, when necessary to meet public health needs. Any instructional and educational materials that are inconsistent with the authorized labeling for REGEN-COV are prohibited. Should the Agency become aware of any instructional or educational materials that are inconsistent with the authorized labeling for REGEN-COV, the Agency will require Regeneron to cease distribution of such instructional and educational materials.

F. Regeneron will report to FDA serious adverse events and all medication errors associated with the use of the authorized REGEN-COV that are reported to Regeneron using either of the following options.

Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

Submitted reports under both options should state: "REGEN-COV use for COVID-19 under Emergency Use Authorization (EUA)." For reports submitted under Option 1, include this language at the beginning of the question "Describe Event" for further analysis. For reports submitted under Option 2, include this language at the beginning of the "Case Narrative" field.

G. All manufacturing facilities will comply with Current Good Manufacturing Practice requirements.

[9] The following types of revisions may be authorized without reissuing this letter: (1) changes to the authorized labeling; (2) non-substantive editorial corrections to this letter; (3) new types of authorized labeling, including new fact sheets; (4) new carton/container labels; (5) expiration dating extensions; (6) changes to manufacturing processes, including tests or other authorized components of manufacturing; (7) new conditions of authorization to require data collection or study; (8) new strengths of the authorized product, new product sources (e.g., of active pharmaceutical ingredient) or of product components. For changes to the authorization, including the authorized labeling, of the type listed in (3), (6), (7), or (8), review and concurrence is required from the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER and the Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist.

H. Regeneron will submit information to the Agency within three working days of receipt of any information concerning any batch of REGEN-COV (whether the batch is distributed or not), as follows: (1) information concerning any incident that causes the product or its labeling to be mistaken for, or applied to, another article; and (2) information concerning any microbiological contamination, or any significant chemical, physical, or other change in deterioration in the product, or any failure of one or more batches of the product to meet the established specifications. Regeneron will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, Regeneron must recall them.

I. Regeneron will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product without notification to and concurrence by the Agency as described under condition D.

J. Regeneron will manufacture and test casirivimab and imdevimab per the process and methods, including in-process sampling and testing and finishing product testing (release and stability) to meet all specifications as detailed in Regeneron's EUA request.

K. Regeneron will list the single dose pack bag containing casirivimab and imdevimab with a unique NDC from the NDCs of the single ingredient listings under the marketing category of Unapproved Drug-Other. As applicable, different vial sizes should be identified by a different package NDC within the product NDC. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at such establishment.

L. Through a process of inventory control, Regeneron and authorized distributor(s) will maintain records regarding distribution of the authorized casirivimab and imdevimab (i.e., lot numbers, quantity, receiving site, receipt date).

M. Regeneron and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

N. Regeneron will establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2. A summary of Regeneron's process should be submitted to the Agency as soon as practicable, but no later than 30 calendar days of the issuance of this letter, and within 30 calendar days of any material changes to such process. Regeneron will provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and, as needed, any follow-up assessments planned or conducted.

O. FDA may require Regeneron to assess the activity of the authorized REGEN-COV against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein). Regeneron will perform the required assessment in a manner and timeframe agreed upon by Regeneron and the Agency. Regeneron will submit to FDA a preliminary

summary report immediately upon completion of its assessment followed by a detailed study report within 30 calendar days of study completion. Regeneron will submit any relevant proposal(s) to revise the authorized labeling based on the results of its assessment, as may be necessary or appropriate based on the foregoing assessment.

Healthcare Facilities to Whom the Authorized REGEN-COV Is Distributed and Healthcare Providers Administering the Authorized Casirivimab and Imdevimab

P. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means, prior to administration of REGEN-COV.

Q. Healthcare facilities and healthcare providers receiving REGEN-COV will track serious adverse events that are considered to be potentially attributable to REGEN-COV use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "REGEN-COV use for COVID-19 under Emergency Use Authorization" at the beginning of the question "Describe Event" for further analysis.

R. Healthcare facilities and healthcare providers will ensure that appropriate storage and cold chain is maintained until the product is administered consistent with the terms of this letter.

S. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized REGEN-COV (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

T. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Regeneron and/or FDA. Such records will be made available to Regeneron, HHS, and FDA for inspection upon request.

U. Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

Conditions Related to Printed Matter, Advertising and Promotion

V. All descriptive printed matter, advertising, and promotional materials relating to the use of the REGEN-COV under this authorization shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

W. No descriptive printed matter, advertising, or promotional materials relating to the use of REGEN-COV may represent or suggest that such products are safe or effective when used

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.

X. All descriptive printed matter, advertising, promotional material, relating to the use of the REGEN-COV clearly and conspicuously shall state that:

- REGEN-COV has not been approved, but has been authorized for emergency use by FDA under an EUA, to treat 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.

- the emergency use of REGEN-COV is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

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RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration