DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761092

BLA APPROVAL

Leadiant Biosciences, Inc.
Attention: GianFranco Fornasini, PhD
Sr. Vice President, Scientific Affairs
9841 Washingtonian Boulevard
Suite 500
Gaithersburg, MD 20878

Dear Dr. Fornasini:

Please refer to your Biologics License Application (BLA) dated October 24, 2017, received October 24, 2017, submitted under section 351(a) of the Public Health Service Act for REVCOVI (elapegademase-lvlr) Injection, 1.6 mg/mL.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2073 to Leadiant Biosciences, Inc., Gaithersburg, Maryland, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product, REVCOVI. REVCOVI is indicated for treatment of Adenosine Deaminase-Severe Combined Immunodeficiency (ADA-SCID).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture recombinant adenosine deaminase (rADA) (b) (4) the elapegademase drug substance (SC-PEG rADA) at (b) (4) The final formulated drug product will be manufactured, filled, labeled, and packaged at Exelead, Inc. 6925 Guion Road, IN 46268. You may label your product with the proprietary name, REVCOVI, and market it in 2.4 mg/1.5 ml in a single-dose vial, injection.

DATING PERIOD

The dating period for REVCOVI shall be 24 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the

formulated drug product. [redacted] (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples of future lots of REVCOVI to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761092**." Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761092. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ADVISORY COMMITTEE

Your application for REVCOVI was not referred to an FDA advisory committee because this biologic is not the first adenosine deaminase enzyme replacement therapy for ADA-SCID and the application did not raise significant safety or efficacy concerns or controversial scientific issues that would benefit from outside expertise or advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, PREA does not apply. Nevertheless, this application included data on pediatric patients.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment, with the timetable you submitted on August 10, 2018, which states that you will conduct this study according to the following schedule:

3497-1 To conduct a study to enroll ADA-SCID naïve patients started on de novo enzyme replacement therapy (ERT) with REVCOVI or converted from Adagen to REVCOVI including patient transitioned from the Study STP-2279-002, over the course of 2 years and continue to follow those patients until the last enrolled patient has 2 years of follow up. Patients who are expected to receive 3 to 4 months of ERT prior to proceeding to hematopoietic stem cell transplantation (HSCT) or gene therapy will be included and contribute data to the analyses.

Draft Protocol Submission:	10/2018
Final Protocol Submission:	01/2019
Study/Trial Completion:	01/2023
Interim Report Submission:	01/2021
Final Report Submission:	07/2023

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments, with the timetable you submitted on October 2, 2018, which states that you will conduct these studies according to the following schedules:

3497-2 To provide data from two additional rADA studies to support the [redacted] (b) (4) hold times of the [redacted] (b) (4) from a microbial control perspective.

Final Report Submission: 02/2020

3497-3 To conduct the bioburden method qualification using one additional batch of the SC-PEG rADA [redacted] bulk drug substance using the same sample volume used in routine testing.

Final Report Submission: 12/2018

3497-4 To perform a study to evaluate the impact of the removal of [redacted] If the data support removal of [redacted] a plan for the removal of [redacted] manufacturing process will be provided. The plan should include an evaluation of consistency of the [redacted] and comparability of elapegademase manufactured with and without [redacted].

Final Report Submission: 07/2019

3497-5 To characterize the purity and stability of end of production cells at full commercial scale for the manufacturing of drug substance [redacted] recombinant adenosine deaminase (rADA).

Final Report Submission: 05/2020

3497-6 To perform a leachable study to evaluate leachables from the manufacturing process and thecontainer closure system in REVCOVI (elapegademase-lvlr) injection drug product and assess potential impact of leachables on product quality. The analysis will be performed using one drug product lot and/or a representative sample (e.g. [redacted]) analyzed at the end of shelf life. Appropriate methods will be used to detect, identify, and qualify organic non-volatile, volatile and semi-volatile species, and [redacted]. Characterization of potential impact on product quality will be assessed using adequate analytical methods. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

Final Report Submission: 12/2021

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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/

JOHN J FARLEY
10/05/2018