DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761065

BLA APPROVAL

TaiMed Biologics USA Corp.
Attention: Helen P. Shu, Ph.D.
VP Regulatory Affairs and Quality
2 Executive Circle, Suite 280
Irvine, CA 92614

Dear Dr. Shu:

Please refer to your Biologics License Application (BLA) dated and received May 3, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for TROGARZO (ibalizumab-uiyk) injection.

We acknowledge receipt of your major amendment dated October 25, 2017, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2057 to TaiMed Biologics USA Corp., Irvine, CA, 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 TROGARZO (ibalizumab-uiyk). TROGARZO is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ibalizumab-uiyk at (b) (4) (b) (4) Final drug product will be labeled and packaged at (b) (4) You may label your product with the proprietary name, TROGARZO, and market it at a strength of 200 mg per 1.33 mL (150 mg/mL) in single-dose vials for injection.

DATING PERIOD

The dating period for TROGARZO shall be 36 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. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of TROGARZO 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.

Any changes in the manufacturing, testing, packaging, or labeling of TROGARZO, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

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, text for patient 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 761065**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for TROGARZO was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for the biologic in the intended population and did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity because TROGARZO (ibalizumab-uiyk) is intended for chronic use in certain HIV-1 infected populations; to identify an unexpected serious risk of developmental and reproductive toxicity as TROGARZO (ibalizumab-uiyk) may be administered to females of reproductive potential; and to assess signals of serious risk due to treatment-emergent resistance substitutions resulting from the use of TROGARZO (ibalizumab-uiyk) in highly treatment-experienced patients who are at risk of developing multidrug resistant HIV-1 infection. Comprehensive and integrated datasets are required to perform an optimal resistance analysis to identify resistance-associated substitutions in patients with virologic failures.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3283-1 Complete and provide a risk assessment of the carcinogenic potential of ibalizumab.

The timetable you submitted on December 14, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2018

3283-2 Submit the final study report for the enhanced pre/postnatal development study in cynomolgus monkeys.

The timetable you submitted on December 14, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2018

3283-3 Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.

The timetable you submitted on February 5, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2018

3283-4 Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: S143P, K171E, N186K/S/R, Q308H/P, G352K/E, and V547A/G.

The timetable you submitted on February 5, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2018

3283-5 Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment in clinical trials TMB-202, entitled *"A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1" (Amended to 24 Week Study)* and TMB-301, *entitled "A Phase 3, Single Arm, 24-Week, Multicenter*

Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1" to better characterize the HIV-1 gp120 sequence at the time of failure.

The timetable you submitted on February 5, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2018

3283-6 Provide integrated virology datasets for clinical trials TMB-202, entitled "*A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1"* (Amended to 24 Week Study) and TMB-301, entitled "*A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1"*. This should include one database for each clinical trial with baseline data for all subjects who were enrolled, and time of virologic failure data for all subjects who failed treatment and were assessed for resistance.

The timetable you submitted on February 5, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2018

Submit clinical protocol(s) to your IND 009776 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your postmarketing commitments:

3283-7 To develop, validate, and implement an appropriate pharmaceutical grade container closure system for ibalizumab bulk drug substance.

The timetable you submitted on February 23, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/2019

3283-8 To perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.

The timetable you submitted on February 23, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2018

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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, please contact Elizabeth Thompson, M.S., Chief, Project Management Staff, at (301) 796-0824 or via email at elizabeth.thompson@fda.hhs.gov.

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 and this page is the manifestation of the electronic signature.

/s/

JOHN J FARLEY
03/06/2018