Our STN: BL 125774/0

BLA APPROVAL
May 19, 2023

Krystal Biotech, Inc.
Attention: Suma Krishnan
2100 Wharton Street, Suite 701
Pittsburgh, PA 15203

Dear Ms. Krishnan:

Please refer to your Biologics License Application (BLA) received June 20, 2022, submitted under section 351(a) of the Public Health Service Act (PHS Act) for beremagene geperpavec-svdt.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2301 to Krystal Biotech,Inc, 2100 Wharton Street, Pittsburgh, PA 15203, under the provisions of section 351(a) of the PHS 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 beremagene geperpavec-svdt, which is indicated for treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain* (*COL7A1*) gene.

The review of this product was associated with the following National Clinical Trial (NCT) number: 04491604.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture beremagene geperpavec-svdt drug substance and drug product through formulation and filling at Krystal Biotech,Inc., 2100 Wharton Street, Pittsburgh, PA 15203. The excipient gel will be manufactured at (b) (4). The final drug product and excipient gel will be labeled, packaged and serialized at (b) (4)

You may label your product with the proprietary name Vyjuvek and market it in cartons containing two single-use vials: one vial containing an extractable volume of 1 mL of beremagene geperpavec-svdt at a concentration of 5 x 10^9 plaque forming units/mL and one vial containing an extractable volume of 1.5 mL of 4.4% hydroxypropyl methylcellulose (HPMC) excipient gel.

ADVISORY COMMITTEE

We did not refer your application to the Cellular, Tissue and Gene Therapies Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for beremagene geperpavec-svdt shall be 12 months from the date of manufacture when stored at (b) (4) -20°C. The dating period for the HPMC excipient gel shall be 12 months from the date of manufacture when stored at -20°C. The date of manufacture shall be defined as the date of vialing of the formulated drug product and excipient gel. The final drug product carton can be stored at the clinical site at 2-8°C for up to 1 month, when not exceeding the dating period of 12 months. We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug product and excipient gel under 21 CFR 601.12.

FDA LOT RELEASE

You are required to submit protocols showing results of all applicable release tests for future lots of beremagene geperpavec-svdt to the Center for Biologics Evaluation and Research (CBER). You may not distribute any lots of product until you receive a notification of release from the Director, CBER.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, 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 the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations :

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of beremagene geperpavec-svdt, or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including the Package Insert submitted under amendment 73, dated May 8, 2023, and the draft carton and container labels submitted under amendment 75, dated May 9, 2023.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the Package Insert submitted on May 8, 2023. Information on submitting SPL files using eLIST may be found in the guidance for industry *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 CONTAINER LABELS

Please electronically submit final printed carton and container labels identical to the carton and container labels submitted on May 9, 2023, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125774/0 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports* at https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm458559.pdf and FDA's Adverse Event reporting System website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher (PRV), as provided under section 529 of the Federal Food, Drug, and Cosmetic Act (FDCA). This PRV has been assigned a tracking number, PRV BLA 125774. 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)(1) 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 PRV must notify FDA of its intent to submit an application with a PRV 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 PRV 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 PRV may be transferred, but each person to whom the PRV 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 PRV, you should refer to this letter as an official record of the voucher. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred.
- FDA may revoke the PRV if the rare pediatric disease product for which the PRV 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 PRV 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 by visiting FDA's Rare Pediatric Disease PRV Program webpage available at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm.

PEDIATRIC REQUIREMENTS

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

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

We acknowledge your written commitments as described in your letters of April 20, 2023 and April 27, 2023 as outlined below:

1. Krystal Biotech commits to reassessing the commercial B-VEC (b) (4) lot release acceptance criteria after data have been collected on (b) (4) commercial lots and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: January 31, 2025

2. Krystal Biotech commits to reassessing the commercial B-VEC COL-7A1 (b) (4) lot release acceptance criterion after data have been collected on (b) (4) commercial lots and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: January 31, 2025

3. Krystal Biotech commits to assessing the consistency of the percentage of the COL7A1 transgene variant (b) (4) in the Phase 3 clinical and Process Performance Qualification (PPQ) B-VEC lots and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

4. Krystal Biotech commits to re-validating the (b) (4) COL7A1 (b) (4) Assay in support of its use for commercial B-VEC lot release. The re-validation will include validating the (b) (4) using appropriate test material and providing the validation results in copies /(b) (4) and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

5. Krystal Biotech commits to performing additional robustness assessments of (b) (4) Quantification of HSV Genome Copy Number by (b) (4) and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

6. Krystal Biotech commits to validating the HPMC concentration assay and implementing this assay, along with an appropriate acceptance criterion, as part of the commercial HPMC gel lot release specification and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

7. Krystal Biotech commits to providing HPMC concentration stability data in support of the current HPMC gel expiry date and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: May 31, 2024

8. Krystal Biotech commits to providing HPMC gel (b) (4) data in support of the current HPMC gel storage, shipping, and labeling conditions and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

9. Krystal Biotech commits to optimize the HSV-1 Plaque Assay to (b) (4) if necessary, and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: May 31, 2024

We request that you submit information concerning chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125774/0. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- a description of what has been accomplished to fulfill the non-section 506B PMC; and

- a summary of any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

POST APPROVAL FEEDBACK MEETING

New biological products 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, please contact the Regulatory Project Manager for this application.

Sincerely,

Melissa Mendoza, JD
Director
Office of Compliance and Biologics Quality
Center for Biologics
Evaluation and Research

Celia Witten, MD
Acting Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics
Evaluation and Research