



Our STN: BLA 125774/0

**MID-CYCLE COMMUNICATION  
SUMMARY**

November 10, 2022

Krystal Biotech, Inc.  
ATTENTION: Suma Krishnan  
2100 Wharton Street  
Pittsburgh, PA 15203

Dear Ms. Krishnan:

Attached is a copy of the summary of your October 14, 2022 Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN 125774/0 in your future submissions related to beremagene geperpavec .

If you have any questions, please contact Rommel Maglalang at [Rommel.Maglalang@fda.hhs.gov](mailto:Rommel.Maglalang@fda.hhs.gov).

Sincerely,

Steven S. Oh, PhD  
Acting Director  
Division of Cellular and Gene Therapies  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research

## Mid-Cycle Communication Teleconference Summary

**Application Type and Number:** BLA 125774/0

**Product Name:** beremagene geperpavec

**Proposed Indication for Use:** Treatment of wounds in patients 6 months and over of age with dystrophic epidermolysis bullosa (DEB)

**Applicant:** Krystal Biotech, Inc.

**Meeting Date & Time:** October 14, 2022, 3:00 pm-4:30 pm

**Committee Chair:** Anna Kwilas, PhD

**RPM:** Rommel Maglalang

### Attendees:

Meghna Alimchandani, MD, CBER/OBPV/DPV

Marie Anderson, CBER/OCBQ/DBSQC/QAB

Kimberly Benton, PhD, CBER/OTAT

Wilson W. Bryan, MD, CBER/OTAT

Dennis Cato, CBER/OCBQ/DIS/BMB

Yongwook Choi, PhD, CBER/OTAT/DCGT

Benjamin Cyge, CBER/OCBQ/DCM/APLB

Donald Ertel, CDR, MS, MT, CBER/OCB/DMPQ

Qianmiao Gao, PhD, CBER/OBPV/DB/TEB

Varsha Garnepudi, CBER/OCBQ/DBSQC/QAB

Denise Gavin, PhD, CBER/OTAT/DCGT

Andrew Harmon, PhD, CBER/OTAT/DCGT

Christopher Jason, MD CBER/OBPV/DE/PB

Anna Kwilas, PhD, CBER/OTAT/DCGT

Carolyn Laurencot, PhD, CBER/OTAT/DCGT

Seung Lee, CDER/DMEPAI

Bo Liang, PhD, CBER/OTAT/DCGT

Wei Liang, PhD, CBER/OTAT

Rommel Maglalang, CBER/OTAT/DRPM

Leyish Minie, MSN, RN, CBER/OTAT/DRPM

Massoud Motamed, PhD, CBER/OTAT/DCGT

CDR Oluwamurewa Oguntimein, PhD, MHS, CPH, MCHES, CDER/DMEPAI

Steven Oh, PhD, CBER/OTAT/DCGT

Most Nahid Parvin, CBER/OCBQ/DBSQC/LBVI

Carl Perez, CBER/OCBQ/DMPQ

Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT

Carolyn Renshaw, CBER/OCBQ/DMPQ

Anne Rowzee, PhD, CBER/OTAT

Douglas Rouse, MD, CBER/OBPV/DPV

Kimberly Schultz, PhD, CBER/OTAT/DCGT

Mercedes Serabian, MS, DABT, CBER/OTAT/DCEPT

Muhammad Shahabuddin, CBER/OCBQ/LBVI

Anurag Sharma, PhD, CBER/OTAT/DCGT

Abigail Shearin, VMD, PhD, CBER/OTAT/DCEPT

Rosa Sherafat-Kazemzadeh, MD, CBER/OTAT/DCEPT  
Ramani Sista, PhD, CBER/OTAT/DRPM  
Cinque Soto, PhD, CBER/OTAT/DCGT  
Million Tegenge, PhD, CBER/OTAT/DCEPT  
Edward Thompson, CBER/OTAT/DRPM  
Tran Triet, PharmD, CBER/OCBQ/BMB  
Lori Tull, CBER/OTOAT/DRPM  
Ramjay Vatsan, PhD, CBER/OTAT/DCGT  
Jianyang Wang, PhD, OTAT/DCGT/GTB  
Wei Wang, PhD, CBER/OCBQ/DMPQ/MRB3  
Claire Wernly, PhD, CBER/OCBQ/DBSQ/LMIVTS  
Lei Xu, MD, PhD, CBER/OTAT/DCEPT  
Iryna Zubkova, PhD, CBER/OCBQ/DMPQ/ARB

### Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.
  - a. Chemistry, Manufacturing, and Controls:
    - i. There are outstanding issues with the drug substance process characterization studies including inadequate qualification of the scale-down model and establishment method(s) for the process parameter ranges.

#### Meeting Discussion:

The applicant provided an overview of their small-scale model assessment. The applicant sampled (b) (4) from (b) (4) commercial scale batch and (b) (4) small-scale runs (b) (4). A qualitative comparison of critical quality attributes (CQAs) between the commercial scale and the small-scale runs was performed. The applicant concluded that their small-scale is representative of the commercial scale process. FDA indicated that the CQA values from the commercial scale did not fall into the ranges of the CQA values from the small-scale runs and the data were not sufficient to demonstrate comparability of the small-scale model and the commercial scale. The applicant recognized the differences and clarified that data from (b) (4) scales were used in the modeling to establish process parameter ranges to account for any differences between the small-scale and commercial scale processes.

FDA expressed concerns with the scale-down model and asked the applicant to provide a rationale for using data from (b) (4) commercial

scale run to demonstrate similar responses to changes in process parameters for the (b) (4) scales. FDA requested that the applicant provide additional correlation data as further justification. The applicant clarified that data from (b) (4) commercial scale runs are available to assess the difference between the commercial and small-scale processes and demonstrate the correlation. FDA requested that the applicant provide these data, ideally presented as dot plots as shown in their slide #5 presented during the external mid-cycle meeting, in response to a follow-up IR to facilitate their review.

FDA noted that the data from the (b) (4) commercial scale run correlated much better with the data from the small scale runs compared to the data from the previous commercial scale runs. The applicant responded by stating that the variability was due the use of (b) (4), and not due to the process. The applicant clarified that (b) (4) was used in the small-scale runs and the (b) (4) commercial scale run, but not in the previous commercial scale runs. The applicant was unsure of the timing of the runs, but agreed to provide this information in response to a future IR.

FDA further stated that they do not agree with the applicant's current approach to set the process parameter ranges using Phase 3 lot release criteria because they are too wide. FDA also did not recommend using the currently proposed commercial acceptance criteria to set the process parameter ranges. Rather, FDA recommends using actual Phase 3 lot release data to set the process parameter ranges. FDA notified the applicant that an IR will be sent requesting that the process parameter ranges be revised accordingly.

- ii. The proposed (b) (4) hold time ranges are not adequately justified because the scale-down model used in the cumulative hold time study is inadequately qualified and the hold time ranges implemented during process validation are not sufficient to support the proposed commercial ranges.

**Meeting Discussion:**

The applicant provided an overview of the hold-time study. The applicant concluded that no (b) (4) hold times resulted in CQAs falling below the lower acceptable limits. These data were used to establish the maximum (b) (4) hold times presented in the BLA.

FDA referred to the earlier discussion on the scale-down model and stated that they were concerned that the stability profile of the scale-down process intermediates may not be representative of the stability profile of

the commercial scale intermediates. Thus, the data provided are not sufficient to justify the proposed extended hold time.

The applicant indicated that clinical lot data, in combination with the small-scale data supported the proposed hold times. FDA stated that an IR will be sent requesting these additional supportive data.

- iii. Drug product filled vials are not labeled at the Ancoris facility prior to being shipped to (b) (4). Identity testing is performed on the (b) (4) vials but is not performed again following labeling. This is inadequate as 21 CFR 610.14 stipulates that product identity must be confirmed on the contents of the final labeled container.

**Meeting Discussion:**

The applicant proposed to ship labeled and packaged product from each lot from (b) (4) to Krystal Biotech where the identity would be confirmed. The shelf carton would be inspected for labeling and the contents of the product vial would be tested for identity via (b) (4).

FDA stated that the (b) (4) alone is inadequate to confirm product identity and requested additional identity testing, for example, including the (b) (4) assay for virus identification.

FDA clarified that according to 21 CFR, identity testing must be performed on the final labeled product. In response, the applicant proposed to perform the (b) (4) assays on the labeled and packaged product alone and not on the unlabeled vial product prior to shipment to (b) (4). FDA advised the applicant to submit this proposal in writing in response to the upcoming IR and FDA will review it upon receipt.

- iv. The HMPC Gel is not being tested for identity and concentration of Methocel as a part of release and stability testing. Testing for identity and Methocel concentration is necessary to support process validation and HPMC Gel stability.
- v. There is limited stability indicating capacity of the current HPMC Gel stability testing.

**Meeting Discussion:**

The applicant reiterated that the function of the gel is to make the product viscous to facilitate application and that gel viscosity and methocel concentration are linearly related. The applicant stated that a specific identity test is not needed for the HPMC gel because the viscosity measurement controls for this CQA as well as HPMC concentration.

FDA stated that identity testing is still needed and requested robust data supporting that the methocel concentration correlates with gel viscosity in the absence of concentration testing. FDA stated that data from (b) (4) studies may also support a lack of concentration testing. The applicant acknowledged FDA's request and plans to add identity testing and submit concentration correlation data. The applicant stated that the potential identity test method is (b) (4)

b. Human Factor Study Protocol, Labeling and Instructions for Use:

- i. We note your Prescribing Information (PI) section 2 Dosage and Administration states, "VYJUVEK should be (b) (4) administered by a Healthcare Professional (HCP)," however, you have not conducted any human factors (HF) validation study to support the use of the intend-to-market commercial product by the intended users (i.e., HCP) in the intended use environment. Specifically, you have not conducted an HF validation study to support (b) (4) of the intend-to-market commercial product by HCPs in the intended use environment. As such, you will not be able to include the statement, '(b) (4)' in your PI, since this has not been validated.

**Meeting Discussion:**

The applicant acknowledged the above statement.

- ii. We note you conducted an HF study (Protocol PRO-HF-01) to support the open-label extension (Protocol B-VEC-EX-02) of the Phase 3 study, which evaluated (b) (4). In this study, Pharmacists mixed the product in the pharmacy. As such, please revise the Dosage and Administration section of the PI to specify that mixing of VYJUVEK should be conducted in the Pharmacy by a Pharmacist.

**Meeting Discussion:**

The applicant clarified that mixing is primarily performed by clinical research coordinators and pharmacy technicians (referred to as authorized designees). Training of the authorized designees occurs at academic institutions and private clinical sites of which a pharmacy or pharmacist are on site. The applicant concluded that the instructions provided in the PI are more than sufficient to support (b) (4) who has a more extensive training background. The applicant requested that the Dosage and Administration language in the PI remain as it is.

FDA acknowledged that it is likely the pharmacy personnel, such as pharmacy technicians, will be the intended users expected to mix the product post-approval.

FDA clarified that available data from the completed HF study supports the HCP administration of the product. However, there are no HF study data that support the (b) (4) of the product since the HF validation study (PRO-HF-02) that is intended to support (b) (4) of the intended-to-market commercial product by HCPs has not been conducted yet. Further, FDA indicated that all statements in the PI need to be supported by available data.

- iii. You submitted an HF validation study protocol (PRO-HF-02) in your Biologics License Application (BLA) to support (b) (4) of the intend-to-market commercial product by HCPs in the intended use environment. However, since you have not conducted the study at this time, we recommend you withdraw your HF validation protocol (PRO-HF-02) from this BLA submission.

#### **Meeting Discussion:**

FDA stated that it is not recommended to submit the HF validation study protocol (PRO-HF-02) under the BLA because there is not enough time to conduct the study and submit the study data for FDA to review within the BLA review cycle.

FDA indicated that the Agency is willing to provide feedback on the protocol. However, FDA recommended the applicant withdraw this protocol from the BLA and submit the revised protocol to the IND after incorporating FDA's comments that would be sent to the applicant as an information request. If data from the HF study, PRO-HF-02, support the (b) (4) of the product by HCPs, the applicant can submit these data with an updated PI in a future prior approval supplement if the initial BLA were to be approved.

#### **2. Information regarding major safety concerns.**

- a. The review team has not identified any major safety concerns at this point.
- b. Please submit the required 120-day safety update.

#### **3. Preliminary Review Committee thinking regarding risk management.**

The review team has not identified a need for REMS at this time.

#### **4. Any information requests sent, and responses not received.**

None

**5. Any new information requests to be communicated.**

As review continues, new information requests will be conveyed as warranted.

**6. Proposed dates for the Late-Cycle meeting (LCM).**

- a. The LCM between you and the Review Committee is currently scheduled for December 15, 2022, 2:00pm-3:30pm.
- b. We intend to send the LCM meeting materials to you approximately 10 days in advance of the LCM.
- c. If these timelines change, we will communicate updates to you during the course of the review.

**7. Updates regarding plans for the AC meeting.**

There are no plans currently to hold an Advisory Committee meeting for this application.

**8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.**

- a. Tentative PMR/PMC Study and Labeling target date – January 19, 2023