



Our STN: BLA 125774/0

**LATE-CYCLE
MEETING MEMORANDUM**
January 12, 2023

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

Dear Ms. Krishnan:

Attached is a copy of the memorandum summarizing your December 15, 2022 Late-Cycle Meeting teleconference with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Rommel Maglalang at Rommel.Maglalang@fda.hhs.gov.

Sincerely,

Heather Lombardi, PhD
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: December 15, 2022; 2pm-3:30pm
Meeting Location: Teleconference (via Zoom)

Application Number: 125774/0
Product Name: VYJUVEK (beremagene geperpavec)
Proposed Indications: Treatment of wounds in patients 6 months and over of age with dystrophic epidermolysis bullosa (DEB)

Applicant Name: Krystal Biotech, Inc.

Meeting Chair: Anna Kwilas, PhD
Meeting Recorder: Rommel Maglalang

FDA ATTENDEES:

Meghna Alimchandani, MD, CBER/OBPV/DPVa
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Wilson W. Bryan, MD, CBE/OTAT
Dennis Cato, CBER/OCBQ/DIS/BMB
Theresa Chen, PhD, CBER/OTAT/DCEPT
Yongwook Choi, PhD, CBER/OTAT/DCGT
Benjamin Cyge, CBER/OCBQ/DCM/APLB
Tianjiao Dai, PhD, CBER/OBPV/DB
Qianmiao Gao, PhD, CBER/OBPV/DB/TEB
Varsha Garnepudi, PhD, CBER/OCBQ/DBSQC
Denise Gavin, PhD, CBER/OTAT/DCGT
Brendan Day, MD, CBER/OBPV/DPV/PB2
Donald Ertel, CDR, CBER/OCBQ/DMPQ
Jie He, CBER/OCBQ/DMPQ
Ning Hu, MD, CBER/OTAT/DCEPT
Adnan A. Jaigirdar, MD, CBER/OTAT/DCEPT
Zhen Jiang, PhD, CBER/OBPV
Anna Kwilas, PhD, CBER/OTAT/DCGT
Carolyn Laurencot, PhD, CBER/OTAT/DCGT
Shiowjen Lee, PhD, CBER/OBPV
Bo Liang, PhD, CBER/OTAT/DCGT
Heather Lombardi, PhD, CBER/OTAT/DCGT
Rommel Maglalang, CBER/OTAT/DRPM
Iris Marklein, PhD, CBER/OTAT/DCGT
Massoud Motamed, PhD, CBER/OTAT/DCGT
Leyish Minie, MSN, RN, CBER/OTAT/DRPM
Narayan Nair, MD, CBER/OBPV/DE
Steven Oh, PhD, CBER/OTAT/DCGT
Most Parvin, PhD, CBER/OCBQ/DBSQC/LFVI

Carl Perez, CBER/OCBQ/DMPQ/MRB3
Graeme Price, PhD, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Douglas Rouse, MD, CBER/OBPV/DPV/PB2
Sandhya Sanduja, PhD, CBER/OTAT/DCEPT
John Scott, PhD, MA, CBER/OBPV/DB
Kimberly Schultz, PhD, CBER/OTAT/DCGT
Mercedes Serabian, MS, DABT, CBER/OTAT/DCEPT
Rosa Sherafat-Kazemzadeh, MD, CBER/OTAT/DCEPT
Ramani Sista, PhD, CBER/OTAT/DRPM
Cinque Soto, PhD, CBER/OTAT/DCGT
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Edward Thompson, CBER/OTAT/DRPM
Triet Tran, PharmD, CBER/OCBQ/DIS/BMB
Nicole Trudel, CBER/OCBQ/DMPQ
Lori Tull, CBER/OTAT/DRPM
Anurag Sharma, PhD, CBER/OTAT/DCGT
Abigail Shearin, VMD, PhD, CBER/OTAT/DCEPT
Jianyang Wang, PhD, OTAT/DCGT/GTB
Wei Wang, PhD, OCBQ/DMPQ
Claire Wernly, PhD, CBER/OCBQ/DBSQC
Lei Xu, MD, PhD, CBER/OTAT/DCEPT
Iryna Zubkova, PhD, CBER/OCBQ/DMPQ

APPLICANT ATTENDEES:

Suma Krishnan, President Research and Development
Hubert Chen, Senior Vice President Clinical Development
Brittani Agostini, Associate Director of Clinical Operations
SaraBeth Hahn, Vice President of Regulatory Affairs
Rachael Borromeo, Director of Regulatory CMC
Devon Christman, Regulatory Affairs Associate
Ram Kamineni, Senior Vice President of CMC and Technical Operations
Carrie Miller, Senior Director of Quality Control
Felino Obillo, Vice President of Operations
Catherine Trumpower, Senior Director of Project Management
S.D. Yogesha, Senior Director of Manufacturing Sciences
Mark Petrich, Vice President of Process Development and Validation
Justin Miller, Process Validation Engineer
Erik Schneider, Senior Manager of Downstream Process
Trevor Parry, Vice President of Research and Scientific Affairs
Rekha Gyanchandani, Director of Analytical Development

BACKGROUND

BLA 125774/0 was submitted on June 20, 2022, for beremagene geperpavec .

Proposed indication: Treatment of wounds in patients 6 months and over of age with dystrophic epidermolysis bullosa

PDUFA goal date: February 17, 2023

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on December 5, 2022.

DISCUSSION

1. Discussion of Substantive Review Issues

A. Chemistry, Manufacturing, and Controls:

- i. During inspection of the Krystal Ancoris facility, inspectors identified that Krystal has implemented a (b) (4) unit in the VYJUVEK (b) (4) unit operation. The process utilizing this new equipment is intended to be the commercial process. However, this equipment was not used to manufacture the PPQ runs. Furthermore, there is no other data in the BLA supporting the comparability of this process with the validated process.

The information needed to support this change has been requested in CMC IR#6, dated December 5, 2022. This information will need to be submitted no later than December 20, 2022, as requested, to facilitate the review process.

Meeting Discussion:

Krystal Biotech stated that the above requested information will be submitted no later than December 20, 2022. The applicant provided a slide presentation detailing the (b) (4) process step. The applicant stated the (b) (4) objectives are to (b) (4). The applicant has determined (via risk assessment and process validation) that the (b) (4) process change is a low-risk change. However, the applicant ran 3 full scale batches as a precaution to support justification (b) (4) change. Full details of the 3 full scale batch runs will be provided in the responses to CMC IR #6, by December 20, 2022.

FDA wanted to confirm if the limits presented in the 3 full scale batch slides are the same in-process limits as what was agreed upon. The applicant confirmed that limits presented in the slides are the same as the agreed upon in-process limits.

FDA requested an explanation of the 2 data points that are out of range in the (b) (4) graph. The applicant recognized that the 2 data points (batch (b) (4) and batch (b) (4)) were outside the comparability range but noted they were still within the specification range. The applicant stated that there will be an investigation as to why the 2 data points are out of range for comparability. The investigation details will be provided in the response to the IR. The applicant believes this discrepancy is due to assay variability and not product variability.

- ii. The (b) (4) process development studies used to support the process characterization are not adequately qualified. The

data provided in the BLA submission are not sufficient to demonstrate that the small-scale models are representative of the commercial scale manufacturing process.

Meeting Discussion:

The applicant stated that their approach to the small-scale model qualification was discussed through amendments and at the Mid-Cycle meeting and believed FDA had no further issues with it. The applicant stated there is no additional data to present.

FDA stated that they concluded that the data provided is not sufficient and the small-scale model is not representative of the commercial scale process. The statistical analysis of the historical data was not appropriate and therefore, the small-scale model is not adequately qualified.

The applicant recognized that the small-scale model does not align directly with the full-scale commercial model. The applicant does acknowledge that more data from the small-scale model could have been obtained but did not feel it was necessary at the time. However, the applicant stated that they believed combining the results from the small-scale batches and (b) (4) commercial scale batches would be sufficient.

FDA understood the applicant's position but stated that in the future, more process development data would need to be provided. The applicant understood this statement.

- iii. The acceptable process parameters ranges are set too wide due to the wide in-process limits used to define the parameter ranges.

Meeting Discussion:

The applicant stated that revised in-process limits, based Phase 3 clinical lot release data and statistical analysis, after removal of outliers was submitted in an IR response on October 12, 2022. The applicant stated that re-calculated CPP acceptable ranges using agreed revised in-process limits were submitted on November 26, 2022. The applicant felt this topic was adequately addressed.

FDA noted that although there was substantial narrowing of in-process limits, there was very little change in the process parameter ranges. FDA stated that this was unexpected and led them to confirm that the statistical model used to set the process parameter ranges was not appropriate and the small scale models used for process development was not adequately qualified. Thus, FDA requested that the applicant set the process parameter ranges based on the empirical data from the PPQ and Phase 3 batches.

The applicant stated that they will explain in more detail in the IR response. However, the applicant noted the reason for the narrowing of the in-process limits not significantly impacting the process parameters ranges is because the agreed (b) (4) range did not change and thus, the changes did not have a large impact on the process limits. FDA noted that although the range of (b) (4) did not change, the in-process limits of other attributes, for example, the (b) (4), that is expected to correlate with (b) (4), were narrowed substantially, which should have affected the other process parameter ranges.

FDA stated that an IR will be sent with a more detailed explanation but reiterated that the FDA does not agree with the statistical modeling methods used to develop the in-process limits. Thus, FDA would like the applicant to recalculate the limits based on the empirical data available and not rely on the chosen statistical model. The applicant acknowledged this statement. FDA also clarified that empirical data from Phase 3 pivotal study batches and additional batches manufactured using the commercial process could be used for these calculations.

- iv. Currently the HPMC Gel (excipient gel) is not being tested for concentration of HPMC (Methocel) as a part of release and stability testing. The testing for HPMC concentration is necessary to support process validation and HPMC Gel stability. HPMC concentration testing should be implemented as part of commercial lot release and stability testing and retrospectively applied to lots used to support a proposed commercial acceptance criterion.

Meeting Discussion:

The applicant stated that two methods for measuring HPMC concentration are in development: (b) (4)

(b) (4) The applicant emphasized the primary attribute is viscosity as the function of the gel is to hold the KB103 in place such that proper patient administration can be accomplished. The applicant has also presented slides demonstrating that HPMC concentration from (b) (4) had no pharmacological effect of KB103 in the wound bed.

FDA understood that concentration affects viscosity, however as provided in responses to previous IRs, there were some HPMC gel batches that showed lower HPMC concentration with higher viscosity. FDA expressed concern that there is not enough data to justify that the HPMC can be consistently manufactured.

The applicant stated that the gel lot discrepancy was addressed in the response to CMC IR 5, in which a (b) (4) gel manufactured by (b) (4)

(which the applicant is no longer using as the gel manufacturer) was shown to have a high viscosity. The applicant stated that the cause of the high viscosity was due to a container closure issue in which there was a loss of (b) (4) during (b) (4). The applicant stated that lots manufactured after this showed consistent data. FDA has acknowledged and reviewed the applicant's response to CMC IR 5 but still remains concerned regarding HMPC gel manufacturing consistency.

FDA stated that the applicant will need to submit the methodology along with data to support the chosen concentration assay. The applicant stated that information on the (b) (4) analysis method will be submitted, but could not provide a timeline of when data will be submitted. FDA asked the applicant to provide the best estimated timeline they could in their IR response.

B. Division of Manufacturing and Product Quality:

- i. The applicant lacks drug product packaging and labeling validation data. Qualification report to be provided by December 20, 2022.

Meeting Discussion:

The applicant stated that the OQ will be completed, but the PQ will be completed on the first three commercial batches. Serialization was submitted through the package validation, but placebo products were used and therefore not performed under production environment. FDA inquired about shipping qualification data using live product. The applicant stated that simulated shipping qualification data using live product was submitted at the end of October. The applicant stated that they will email the RPM with the date of the submission along with the report number.

2. Discussion of established Pharmacologic Class:

Meeting Discussion:

FDA stated that the pharmacologic class for VYJUVEK will be "a herpes simplex virus Type 1 (HSV-1) vector-based gene therapy". The applicant had no further questions.

Additional Application Data:

Meeting Discussion:

- a. The applicant stated that a response to CMC IR #6 will contain a full description of the validation of the method used to detect vector genomes in clinical studies. Additional data includes the full range of the assay.

- b. The applicant also stated that data from whole genome sequence analysis on three Phase 3 pivotal lots and PPQ lots will be submitted as soon as available. The applicant stated that data on coverage per position and depth of coverage of the whole genome of the *in silico* generated reference genome and the original reference genome (b) (4), a comparison of variant calls (using the *in silico* reference genome) produced by the (b) (4) variant caller versus a viral dataset optimized variant caller, such as (b) (4), as requested in CMC IR #6 will also be provided.
- c. The applicant will also submit a copy of the Phase 3 clinical data recently published in the New England Journal of Medicine and two additional editorials.

4. Information Requests:

Meeting Discussion:

Regarding CMC IR #6, the applicant counter proposed FDA's request to set the HSV plaque titer as (b) (4) PFU/mL for commercial KB103 DP lot release. The applicant asked FDA to consider (b) (4) PFU/mL for commercial KB103 DP lot release. FDA stated that they do not agree with the applicant's counter proposal and insisted on (b) (4) PFU/mL for commercial KB103 DP lot release. FDA stated that the titer should be based on both manufacture of product and Phase 3 clinical data and that the assay variability is already factored into the titer calculation. FDA pointed out that the lowest titer of a Phase 3 clinical lot was (b) (4) PFU/mL. The applicant acknowledged FDA's rationale. The applicant asked if the titer can be calculated from (b) (4) based on stability data. FDA stated that the lot release titer should be based on release testing and not stability testing. The applicant acknowledged this statement and had no further questions.

Regarding CMC IR #6, question 21, the applicant stated that the lower limit of the excipient gel viscosity specification was updated in CMC IR #5 with additional data what will be provided in their response to CMC IR #6. FDA stated that the data will be reviewed upon receipt.

5. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk).

There is no anticipation of a REMS at this time.

Meeting Discussion: There was no discussion from the applicant.

6. Postmarketing Requirements/Postmarketing Commitments

Meeting Discussion:

FDA stated that Postmarketing Commitments (PMC) are being considered pertaining to a number of topics discussed, for example: validation of the HPMC concentration assay and additional drug product sequencing data. The applicant acknowledged this statement and had no further questions.

7. Major Labeling Issues

Label review is ongoing. First draft label will be sent to applicant by January 19, 2023.

Meeting Discussion: There was no discussion from the applicant.

8. Review Plans

Label review is ongoing. First draft label will be sent to applicant by January 19, 2023. The BLA review is ongoing.

Meeting Discussion:

The applicant wanted to confirm the Action Due Date as February 17, 2023. The FDA confirmed the current Action Due Date of February 17, 2023.

9. Applicant Questions

Meeting Discussion:

No further questions from the applicant.

10. Wrap-up and Action Items

Meeting Discussion:

FDA reiterated that the Label review is ongoing, the first draft label will be sent to applicant by January 19, 2023 and the BLA review is ongoing. FDA's clinical team requested a status update on the durability of efficacy data. The applicant stated that the durability of efficacy data will be submitted within the next few weeks.

FDA stated that the Pre-Licensure inspection of the Berkshire facility will occur on January 16, 2023 and that there are no other outstanding inspections.

FDA also reminded the applicant that a significant amount of CMC data is expected in the response to CMC IR #6 and that the Action Due Date could be impacted by this submission. FDA also stated that a decision impacting the review timeline will be made within 14 days of receipt of that information (expected on December 20, 2022).

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.