



Our STN: BL 125787/0

**LATE-CYCLE
MEETING SUMMARY**
November 17, 2023

Vertex Pharmaceuticals Inc
Attention: Mr. Brett Richardson
50 Northern Avenue
Boston, MA 02210

Dear Mr. Richardson:

Attached is a copy of the memorandum summarizing your October 19, 2023 Late-Cycle 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 in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) BL 125787/0 in future submissions related to the subject product.

If you have any questions, please contact Hosna Keyvan by email at hosna.keyvan@fda.hhs.gov.

Sincerely,

Mara Miller, MA
Director
Division of Review Management and Regulatory Review 2
Office of Review Management and Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: October 19, 2023 11:00AM-1:00PM (ET)
Meeting Location: Teleconference via Zoom
Application Number: BL 125787/0
Product Name: Exagamglogene autotemcel (exa-cel)
Indication: Treatment of sickle cell disease (SCD) in patients 12 years of age or older
Applicant Name: Vertex Pharmaceuticals Incorporated

Meeting Chair: Anna Kwilas, PhD, CBER/OTP/OGT
Meeting Recorder: Hosna Keyvan, CBER/OTP/ORMRR

FDA ATTENDEES

Meghna Alimchandani, MD, CBER/OBPV/DPV
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Srinivas Ayyala, MD, CBER/OBPV/DPV
Danielle Bauman, CBER/OTP/ORMRR
Muhammad (Umer) Choudhry, MD, CBER/OTP/OCE
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Jessica Chery, PhD, CBER/OTP/OGT
Benjamin Cyge, CBER/OCBQ/DCM/APLB
Tianjiao Dai, PhD, CBER/OBPV/DB
Heather Erdman, MCPM, RAC, CQPA, CBER/OTP/ORMRR
CDR Donald Ertel, MS, MT(ASCP), CBER/OCBQ/DMPQ
Feorillo Galivo, MD, PhD, CBER/OTP/OPT
Denise Gavin, PhD, CBER/OTP/OGT
Elena Gubina, PhD, CBER/OTP/OGT
Leila Hann, CBER/OTP
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Jie He, CBER/OCBQ/DMPQ
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John Scott, PhD, MA, CBER/OBPV/DB
Abigail Shearin, VMD, PhD, CBER/OTP/OPT
Kimberly Schultz, PhD, CBER/OTP/OGT
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Iwen Wu, PhD, CBER/OTP/OPT
Lihan Yan, PhD, CBER/OBPV/DB
Zhaohui Ye, PhD, CBER/OTP/OGT

APPLICANT ATTENDEES

Tony Boitano, PhD
Carmen Bozic, MD
Juliana Muscat, PhD
Jean-Marc Guettier
William Hobbs, MD, PhD
Ciaran Brady
Stephanie Krogmeier, PhD

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Angela Yen, PhD
Michael Chang, BSc
David Altshuler, MD, PhD
Morrey Atkinson, PhD
Brett Richardson, BS, MBA
Andrew Kuzmission, PhD
Christopher Simard, MD
Nia Tatsis, PhD
Leorah Ross, MD
Fengjuan (Joan) Xuan, PhD
Bo Yang, PhD

CRISPR Attendees

Laurie Kelliher, BSc
Phuong Khanh (PK) Morrow, MD

BACKGROUND

BLA 125787/0 was submitted on April 3, 2023

Name of the Biologic: Exagamglogene autotemcel (exa-cel) / Casgevy.

Proposed indication: Treatment of sickle cell disease (SCD) in patients 12 years of age or older

PDUFA goal date: December 8, 2023

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on October 5, 2023 and issued Advisory Committee Briefing Materials on October 5, 2023.

DISCUSSION

1. Discussion of Substantive Review Issues

- a. We note that the presence of visible particulates in exa-cel drug product was discussed during the BLA (b) (4) Midcycle meeting and is currently being addressed.

2. Discussion of Minor Review Issues

- a. Statistical: There are three statistical issues that will affect the treatment effect estimate and confidence interval, but not to a degree sufficient to seriously question the efficacy of exa-cel:
 - i. You defined the PES to include only subjects with at least 16 months of follow-up after exa-cel infusion. While it is reasonable to require a minimum duration of follow-up on a given number of subjects to assess whether the amount of data is ready for BLA submission, it is not reasonable to exclude subjects from efficacy consideration based on the duration of follow-up. In particular, one subject with 14.3 months of follow-up experienced three sVOCs from Months 11.6 to 14.1, and therefore had no chance to meet the definition of VF12 responder with additional follow-up. We consider this subject to belong to PES and to be a VF12 non-responder.
 - ii. You considered death before achieving VF12 due to exa-cel related adverse events as VF12 non-responders. You excluded the one death on Month 8.9, which you stated was due to COVID-19, from the PES. Because we cannot rule out the conditioning regimen in preparation for exa-cel infusion, an integral component of the exa-cel treatment regimen, as a contributing factor, we consider this subject to belong to PES and to be a VF12 non-responder.

The analysis at around 30 subjects corresponds roughly to the 3rd interim analysis in your study, therefore one-sided confidence intervals should be reported with a confidence level of 99.46% corresponding to the planned type 1 error of 0.0054 at the 3rd IA, instead of with an unadjusted confidence level of 95%.

Meeting discussion:

Vertex presented slides provided to the FDA regarding the three points raised by FDA above and requested discussion of an additional proposal regarding confidence level reporting. Below is a summary of FDA's position after further internal discussion:

- i. FDA maintains that Subject (b) (6) should be included as a non-responder in the primary efficacy analysis on VF12 response rate analysis as the response status can be determined for this subject.
 - ii. FDA agrees with the Applicant's previous approach to exclude the subject who died from efficacy analysis.
 - iii. FDA agrees with the Applicant's proposal to consider that only one interim analysis was practically conducted and set the allotted type 1 error rate at one-sided 0.0198. For easier communication, FDA suggests to round the type 1 error rate to 0.02.
 - iv. The Applicant proposed to report confidence intervals (CIs) with two-sided confidence levels of 95%, regardless of the corresponding type 1 error rate. FDA recommends reporting CIs with confidence levels consistent with the significance levels of the corresponding statistical tests. That is, for the primary efficacy analysis on the VF12 response rate, a one-sided 98% CI should be reported. This recommendation aligns with general practice and two guidance documents: (1) ICH E9 Statistical Principles for Clinical Trials (1998) Section 5.6 and (2) Adaptive Designs for Clinical Trials of Drugs and Biologics (2019) Section V.A. In particular, we quote the latter guidance "*To ensure the scientific and statistical credibility of trial results and facilitate important benefit-risk considerations, an approach for calculating estimates and confidence intervals that appropriately accounts for the group sequential design should be prospectively planned and used for reporting results.*"
- b. Clinical: The number of adolescent subjects in the efficacy evaluable population is limited and with a short follow-up period.

Meeting discussion:

This issue is still under consideration at FDA and there is nothing needed from Vertex at this time.

3. Additional Applicant Data

Vertex clarified the locus “hom_ot110” was already included in their off-target assessment, which is why it was not listed among the 50 additional loci that were nominated based only on knowledge of genetic variation. In addition, the nomenclature used to describe the site in Vertex’s documentation is different from that described in the Cancellieri paper because it had been submitted to FDA in 2018 in support of the IND 5 years prior to the publication of the Cancellieri paper in 2023.

FDA acknowledged Vertex’s position that the locus identified in the Cancellieri paper was included in Vertex’s assessment and would consider adding an erratum to correct the FDA’s AdCom briefing book statement.

4. Information Requests

- a. Chemistry, Manufacturing and Controls (CMC) IR #8 due: October 6, 2023
- b. As our review continues, new information requests will be conveyed as needed.

5. Discussion of Upcoming Advisory Committee Meeting

- a. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:
<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

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

- a. The review is ongoing. The need for Risk Evaluation and Mitigation Strategy (REMS), PMRs, or PMCs remains undetermined at this time.

Meeting Discussion:

FDA noted that at this time, the need for a Risk Evaluation and Mitigation Strategy (REMS) is not anticipated.

7. Postmarketing Requirements/Postmarketing Commitments

Chemistry, Manufacturing, and Controls (CMC):

- a. The review is ongoing. The need for post-marketing requirements (PMRs) or post-marketing commitments (PMCs) remains undetermined at this time.

Clinical/Epidemiology:

- b. The review is ongoing. The need for PMRs or PMCs remains undetermined at this time.

8. Major Labeling Issues

Label review is ongoing. Any labeling issues will be discussed during the labeling negotiations.

9. Review Plans

- a. Anticipated PMRs, if applicable, will be communicated following the Advisory Committee meeting.
- b. PMCs will be communicated no later than November 8, 2023.
- c. Label will be sent to Applicant for negotiations no later than November 8, 2023.

10. Applicant Questions

- a. Vertex requested that FDA remove the statement calling into question the 1000 genomes project and asked if FDA would update the briefing book rather than issue a separate erratum published on the FDA website. FDA stated that they would discuss the best way to address the statement in question.
- b. Vertex asked if advisory committee (AC) questions could be shared. FDA stated that the final AC questions would be posted online two days before the meeting.
- c. Vertex asked if this BLA would undergo Accelerated or Traditional approval. FDA stated the review is ongoing, and FDA cannot make any statements at this time regarding Accelerated or Traditional approval.
- d. Vertex asked if there was anything pending that they needed to provide in order to keep the submission on track for the December 8, 2023 PDUFA date. FDA indicated there was nothing pending that would impact the PDUFA date.
- d. Vertex asked about the upcoming CMC informal call. CMC team stated the informal call on October 27, 2023 from 12:30pm to 1:00pm will be to discuss the proposed SPY 101 hold times.

Wrap-up and Action Items

- a. Anticipated PMRs, if applicable, will be communicated following the Advisory Committee meeting.

- b. PMCs will be communicated no later than November 8, 2023.
- c. Label will be sent to Applicant for negotiations no later than November 8, 2023.
- d. FDA will add an erratum to correct the AC briefing book statement.

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.