



Our STN: BL 125785/0

**LATE-CYCLE
MEETING MEMORANDUM**

Vertex Pharmaceuticals Inc
Attention: Brett Richardson
Associate Director, Regulatory Strategy
50 Northern Avenue
Boston, MA 02210

Dear Brett Richardson:

Attached is a copy of the memorandum summarizing your December 18, 2023 Late-Cycle Meeting teleconference with CBER. This memorandum constitutes the official record of the meeting teleconference. If your understanding of the meeting 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) in future submissions related to the subject product.

If you have any questions, please contact Danielle Bauman at (301)796-4501 or by email at danielle.bauman@fda.hhs.gov.

Sincerely,

Beatrice Kallungal, MS
Director
Division of Review Management and Regulatory Review 1
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: December 18, 2023 | 11am – 12pm EST
Application Number: BLA 125785/0
Product Name: Exagamglogene autotemcel (exa-cel)
Indication: Treatment of transfusion-dependent β -thalassemia (TDT) in patients 12 years of age and older
Applicant Name: Vertex Pharmaceuticals Inc
Meeting Chair: Anna Kwilas, PhD
Meeting Recorder: Danielle Bauman, MPH

FDA ATTENDEES

Meghna Alimchandani, MD, CBER/OBPV/DPV
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Srinivas Ayyala, MD, CBER/OBPV/DPV
Danielle Bauman, MPH, CBER/OTP/ORMRR
Theresa Chen, PhD, CBER/OTP/OPT
Jessica Chery, PhD, CBER/OTP/OGT
Muhammad (Umer) Choudhry, MD, CBER/OTP/OCE
Benjamin Cyge, CBER/OCBQ/DCM/APLB
Heather Erdman, MCPM, RAC, CQPA, CBER/OTP/ORMRR
Denise Gavin, PhD, CBER/OTP/OGT
Lin Huo, PhD, CBER/OBPV/DB
Anna Kwilas, PhD, CBER/OTP/OGT
Shiowjen Lee, PhD, CBER/OBPV/DB
Wei Liang, PhD, CBER/OTP
Shuya (Joshua) Lu, PhD, CBER/OBPV/DB
Prasad Mathew, MD, CBER/OTP/OCE
Adamma Mba-Jonas, MD, MPH CBER/OBPV/DPV/PB
Kavita Natrajan, MD, CBER/OTP/OCE
Steven Oh, PhD, CBER/OTP/OCTHT
Most Nahid Parvin, CBER/OCBQ/DBSQC
Carl Perez, CBER/OCBQ/DMPQ
Komudi Singh, PhD, CBER/OTP/OCTHT
Ramani Sista, PhD, CBER/OTP/ORMRR
Triet Tran, PharmD, BCSCP, CBER/OCBQ/DIS
Nicole Verdun, MD, CBER/OTP
Xiaofei Wang, PhD, CBER/OTP/OCE
Lihan Yan, PhD, CBER/OBPV/DB
Zhaohui Ye, PhD, CBER/OTP/OGT

APPLICANT ATTENDEES

Name	Title	Affiliation
Carmen Bozic	Executive Vice President, Chief Medical Officer	Vertex Pharmaceuticals Incorporated
Jean-Marc Guettier	Senior Vice President, Clinical Development	Vertex Pharmaceuticals Incorporated
William Hobbs	Vice President, Clinical Pipeline Development	Vertex Pharmaceuticals Incorporated
Stephanie Krogmeier	Vice President, Global Regulatory Affairs	Vertex Pharmaceuticals Incorporated
Brett Richardson	Associate Director, Regulatory Strategy	Vertex Pharmaceuticals Incorporated
Christopher Simard	Vice President, Patient Safety, Medical Safety and Risk Management	Vertex Pharmaceuticals Incorporated
Nia Tatsis	Executive Vice President, Chief Regulatory and Quality Officer	Vertex Pharmaceuticals Incorporated
Laurie Kelliher	Executive Director, Regulatory Affairs	CRISPR Therapeutics

BACKGROUND

BLA 125785/0 was submitted on March 31, 2023, for Exagamglogene autotemcel.

Proposed indication: Treatment of transfusion-dependent β -thalassemia (TDT) in patients 12 years of age and older

PDUFA goal date: March 30, 2024

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on December 8, 2023.

DISCUSSION

1. Discussion of Substantive Review Issues

At this time, there are no substantive review issues.

2. Discussion of Minor Review Issues?

None

3. Additional Applicant Data

None requested from FDA

4. Information Requests

a. Labeling IR #6 (noted under item #8)

b. Question 1 of Clinical IR #7 – to be submitted by COB December 19, 2023

5. Discussion of Upcoming Advisory Committee Meeting

An Advisory Committee meeting is not planned.

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)

The review is ongoing. We do not anticipate a Risk Evaluation and Mitigation Strategy (REMS) at this time. We have made a preliminary evaluation of anticipated postmarketing requirements and commitments (PMR/PMC) as described in section 7.

7. Postmarketing Requirements/Postmarketing Commitments

Chemistry, Manufacturing, and Controls (CMC):

a. Vertex Pharmaceuticals, Inc., commits to perform a supplemental shipping validation study of exa-cel assessing the quality attributes including

(b) (4)

for (b) (4) transportation samples using the (b) (4)

commercial shippers. The final validation study report will be submitted as a Postmarketing Commitment-Final Study Report by May 31, 2024.

Final Report Submission: May 31, 2024

b. Vertex Pharmaceuticals, Inc., commits to perform a supplemental (b) (4) hold time stability study in which additional data are obtained to support the current hold time proven acceptable ranges, including the cumulative proven acceptable hold time. The final validation study report will be submitted as a Postmarketing Commitment-Final Study Report by December 31, 2024.

Final Report Submission: December 31, 2024

Clinical/Epidemiology/Bioinformatics:

- c. 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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

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 malignancies and off-target effects following genome editing after administration of exa-cel.

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

Therefore, should this product be approved, we have determined that you will be required to conduct the studies described below.

- i. A postmarketing, prospective, multi-center, observational study, to assess and characterize the risks of malignancies and off-target effects following genome editing occurring after treatment with exa-cel, and to assess the long-term safety of exa-cel. The study will include 150 patients with transfusion dependent beta thalassemia (TDT) who received/will receive exa-cel, and each enrolled patient will be followed for 15 years after product administration. The study design will include monitoring (at pre-specified intervals) with adequate testing strategies (Study Protocol VX22-290-101).

Please also confirm your proposed study milestone dates:

Final Protocol Submission: March 31, 2024

Study Completion: December 31, 2042

Final Study Report Submission: December 31, 2043

- o Vertex requested OBPV to add the language to include secondary malignancies.
- ii. Conduct studies to comprehensively assess and screen for the impact of sequence heterogeneity on the risk of off-target editing in the patient population for exagamglogene autotemcel. Specifically:
 - 1. Perform a new in silico off-target analysis using publicly available databases/datasets to allow for inclusion of more variants. Specifically, perform analysis using all variants with at least 0.5% allele frequency in at least one of the 5 continental

groups (Africa, Europe, East Asia, South Asia, and the Americas).

2. Perform confirmatory testing, as appropriate and feasible, of all the off-target loci nominated from the new in silico analysis from (i) as well as those that were not accounted for in the previous study using appropriate samples harboring variants. Specifically:
 - a. Screen for the presence of all previously identified variants (e.g., CPS1) as well as any variants identified in study (i) and (ii) in the patients treated in Studies 121, 111, 141, 151, 161, and 171.
 - b. For patients with a confirmed variant(s), assess for indels and chromosomal changes at each respective locus in appropriate samples.

Final Protocol Submission (submitted): December 1, 2023

Study Completion Date: June 30, 2032

Final Report Submission: June 30, 2032

Please provide your written acknowledgement of the above PMRs.

FDA will send the formal PMR/PMC communication by the end of the day (12/18/23)

8. Major Labeling Issues – Labeling IR #6 sent to applicant 12/11/23 requesting an amended label submitted to BLA 125785 that incorporates the final approved labeling from BLA 125787. Expected December 18 by noon.

Based on SCD BLA labeling advice, Vertex proactively made changes to TDT label

Note for applicant: After negotiation is complete -> the final accepted language should be submitted as an amendment to both the child STN and the parent labeling PAS for simultaneous approval

9. Review Plans
 - a. Anticipated PMRs, if applicable, will be communicated no later than February 3, 2024
 - b. Proposed PMRs/PMCs will be communicated no later than February 29, 2024.
 - c. Label will be sent to Applicant for negotiations no later than February 29, 2024.

10. Applicant Questions

- a. Applicant questioned the review timeline and if FDA will be approving early. FDA could not comment. The review is ongoing and the Agency is still on-target for the PDUFA ADD of March 30, 2024.
- b. Applicant asked how the BLAs will be handled after action is taken on 125785. FDA explained that if the BLA is approved, 125785 will be closed and rolled over into a supplement under 125787.

11. Wrap-up and Action Items

- a. Expect amended label after the meeting
- b. Expect the response to Q1 for clinical IR #7 by COB Tuesday, December 19, 2023.
- c. PMRs/PMCs will be formally communicated.

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.