



STN: BL 125787/0

**MID-CYCLE COMMUNICATION
SUMMARY**
August 29, 2023

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

Dear Mr. Richardson:

Attached is a copy of the Summary for your July 31, 2023 Mid-Cycle Communication Teleconference with CBER.

Please include a reference to STN BL 125787/0 in your future submissions related to the subject product.

If you have any questions, please contact Hosna Keyvan at (240) 762-8645 or 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

Mid-Cycle Communication Teleconference Summary

Application Type and Number: BLA 125787/0
Product Name: Exagamglogene autotemcel (exa-cel)
Proposed Indication for Use: Treatment of sickle cell disease (SCD)
Applicant: Vertex Pharmaceuticals Incorporated
Meeting Date & Time: July 31, 2023, 1:30 PM - 3:30 PM
Committee Chair: Anna Kwilas
RPM: Hosna Keyvan

FDA Attendees:

Hoda Abadeer, CBER/OCBQ/DMPQ
Meghna Alimchandani, MD, CBER/OBPV/DPV
Srinivas Ayyala, MD, CBER/OBPV/DPV
Danielle Bauman, CBER/OTP/ORMRR
Juliane Carvalho, MS, RAC, CBER/OTP/ORMRR
Dennis Cato, CBER/OCBQ/DIS/BMB
Muhammad Choudhry, MD, CBER/OTP/OCE
Monique Cortez, MS, CBER/OTP/ORMRR
Benjamin Cyge, CBER/OCBQ/DCM/APLB
Tianjiao Dai, PhD, CBER/OBPV/DB
Heather Erdman, MCPM, RAC, CQPA, CBER/OTP/ORMRR
Donald Ertel, CBER/OCBQ/DMPQ
Andrew Harmon, PhD, CBER/OTP/OGT
Jie He, CBER/OCBQ/DMPQ
Jana Highsmith, CBER/OCBQ/DMPQ
Lin Huo, PhD, CBER/OBPV/DB
Timothy Kamaldinov, PhD, CBER/OTP/OGT
Karl Kasamon, MD, CBER/OTP/OCE
Megha Kaushal, MD, CBER/OTP/OCE
Hosna Keyvan, CBER/OTP/ORMRR
Christine Knoll, MD, CBER/OTP/OCE
Hyesuk Kong, PhD, CBER/OCBQ/DBSQC
Anna Kwilas, PhD, CBER/OTP/OGT
Linda Le, MBA, CBER/OTP/ORMRR
Shuya (Joshua) Lu, PhD, CBER/OBPV/DB
Yuqun Abigail Luo, PhD, CBER/OBPV/DB
Wei Liang, PhD, CBER/OTP
Prasad Mathew, MD, CBER/OTP/OCE
Adamma Mba-Jonas, MD, MPH CBER/OBPV/DPV/PB
Mara Miller, MA, CBER/OTP/ORMRR
Leyish Minie, MSN, RN, CBER/OTP/ORMRR
Narayan Nair, MD, CBER/OBPV/DPV
Kavita Natrajan, MD, CBER/OTP/OCE
Tao Pan, PhD, CBER/OCBQ/DBSQC

Most Nahid Parvin, CBER/OCBQ/DBSQC
Carolyn Renshaw, CBER/OCBQ/DMPQ
Kimberly Schultz, PhD, CBER/OTP/OGT
John Scott, PhD, MA, CBER/OBPV/DB
Abigail Shearin, VMD, PhD, CBER/OTP/OPT
Komudi Singh, PhD, CBER/OTP/OCTHT
Cinque Soto, PhD, CBER/OTP/OCTHT
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB
Brian Stultz, MS, CBER/OTP/OGT
Triet Tran, CBER/OCBQ/DIS
Million Tegenge, PhD, CBER/OTP/OCE
Edward Thompson, CBER/OTP/ORMRR
Lori Tull, CBER/OTP/ORMRR
Prajakta Varadkar, CBER/OCBQ/DMPQ
Nicole Verdun, MD, CBER/OTP
Xiaofei Wang, PhD, CBER/OTP/OCE
Lihan Yan, PhD, CBER/OBPV/DB

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.
 - a. Chemistry, Manufacturing, and Controls (CMC):
 - i. Disagreement on the proposed exa-cel potency assay.
 - ii. Disagreement on the adequacy of the (b) (4) -based identity assay validation and identity confirmation acceptance criteria.
 - b. Bioinformatics:
 - i. Lack of consensus off-targets between biological replicates potentially due to different dsODN concentrations used or genetic heterogeneity is unresolved.
 - c. Clinical:
 - i. Adequacy of the small amount of data on adolescent subjects. Implications of this issue are under review.
 - d. Statistical:
 - i. Implication on interpretation of trial results of frequent and late changes in draft statistical analysis plan (SAP) proposed in

meetings without submission as IND amendments. The only stand-alone version of SAP was submitted to the BLA only.

- a. Adequacy of error probability control.
- b. The SAP in the BLA contains new substantive elements that FDA would not agree to, e.g., counting time periods separated by periods confounded by use of prohibited medications as consecutive periods in determination of VF12, the primary efficacy endpoint.
- c. You set the null hypothesis on the VF12 endpoint at 50% response rate without including supporting rationales in the protocol or SAP. It is unclear the 50% null hypothesis is adequate. At this time, please submit your supporting rationale to the BLA, taking into consideration of factors that may influence the null response rate, e.g., subject characteristics, definition of the analysis set and VF12 endpoint, etc.
- d. A single clinical site contributes a substantial proportion of subjects to the primary analysis set and its result shows considerable difference from the combined result from the remaining sites. The implication of this observation is under review.

Discussion of statistical issues: The sponsor will submit a summary of the evolution of the protocol and SAP, including information on timeline relative to the clinical trial progression and important agreements and disagreements. FDA will share more information regarding the site difference indicted in item 1.d.i.d above.

2. Information regarding major safety concerns.

- a. Delayed platelet engraftment (compared with allogeneic transplant).
 - b. Lack of reduction in rate of VOCs during mobilization period (considering subjects were heavily transfused rendering their HbS% into sickle-trait range).
3. Preliminary Review Committee thinking regarding a.) risk management, b) the potential need for any post-marketing requirement(s) (PMRs), and c.) the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk.

- a. Review is ongoing. The need for Risk Evaluation and Mitigation Strategy (REMS), PMR or PMC remains undetermined at this juncture.
4. Any information requests (IR) sent, and responses not received.
 - a. CMC IR sent July 21, 2023, due August 4, 2023 (Received on August 4, 2023).
 - b. Clinical IR sent July 26, 2023, due August 2, 2023 (Received on August 2, 2023).
5. Any new information requests to be communicated.
 - a. As our review continues, new information requests will be conveyed as needed.
 - b. Bioinformatics will send an IR pertaining to:
 - i. the (b) (4) used in preclinical studies and the final DP, and
 - ii. demographic information for HSPCs donors that were used in preclinical studies.
6. Proposed date for the Late-Cycle meeting (LCM).
 - a. The LCM between you and the Review Committee is currently scheduled for October 19, 2023, from 11:00AM – 1:00PM (ET). We intend to send the LCM meeting materials to you by October 5, 2023.

If these timelines change, we will communicate updates to you during the course of the review.
7. Updates regarding plans for the AC meeting.
 - a. The scheduled date for the Advisory Committee (AC) meeting is October 31, 2023.
8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates, and notification of intent to inspect manufacturing facilities.
 - a. External Late-Cycle Meeting Oct 19, 2023
 - b. Communicate Anticipated PMRs Oct 27, 2023
 - c. Communicate Proposed Labeling and PMCs Nov 8, 2023
 - d. Send FDA Action Letter Dec 8, 2023

Tentative Inspection Schedule:

- a. Inspection of (b) (4) is scheduled for (b) (4)
- b. Inspection of (b) (4) is scheduled for (b) (4)
- c. Inspection of (b) (4) is scheduled for (b) (4).
- d. Inspection (704(a)(4) facility records review in lieu of inspection) of (b) (4) is in progress.
- e. (b) (4) DP (exa-cel) manufacturing, labeling, release and stability testing (except potency, on-target editing, sterility, mycoplasma), packaging, and storage. PLI (b) (4)