



Our STN: BL 125785/0

**MID-CYCLE COMMUNICATION
SUMMARY**

October 27, 2023

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

Dear Mr. Richardson:

Attached is a copy of the summary of your September 28, 2023 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 BL 125785/0 in your future submissions related to Exagamglogene autotemcel (exa-cel).

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

Mid-Cycle Communication Teleconference Summary

Application Type and Number: BLA 125785/0
Product Name: Exagamglogene autotemcel (exa-cel)
Proposed Indication for Use: Treatment of transfusion-dependent β -thalassemia (TDT) in patients 12 years of age and older
Applicant: Vertex Pharmaceuticals Incorporated
Meeting Date & Time: September 28, 2023, 1:30 pm to 2:30 pm
Committee Chair: Anna Kwilas
RPM: Danielle Bauman

Attendees:

Danielle Bauman, CBER/OTP/ORMRR
Jessica Chery, PhD, CBER/OTP/OGT
Muhammad Choudhry, MD, MS, CBER/OTP/OCE
Heather Erdman, MCPM, RAC, CQPA, CBER/OTP/ORMRR
CDR Donald Ertel, MS, MT(ASCP), CBER/OCBQ/DMPQ
Denise Gavin, PhD, CBER/OTP/OGT
Jana Highsmith, CBER/OCBQ/DMPQ
Hosna Keyvan, CBER/OTP/ORMRR
Anna Kwilas, PhD, CBER/OTP/OGT
Eric Levenson, PhD, CBER/OTP/OGT
Prasad Mathew, MD, CBER/OTP/OCE
Kavita Natrajan, MD, CBER/OTP/OCE
Carl Perez, CBER/OCBQ/DMPQ
Gregory Price, PhD, CBER/OCBQ/DMPQ
Carolyn Renshaw, CBER/OCBQ/DMPQ
Kimberly Schultz, PhD, CBER/OTP/OGT
Komudi Singh, PhD, CBER/OTP/OCTHT
Ramani Sista, PhD, CBER/OTP/ORMRR
Cinque Soto, PhD, CBER/OTP/OCTHT
Brian Stultz, MS, CBER/OTP/OGT
Nicole Verdun, MD, CBER/OTP
Xiaofei Wang, PhD, CBER/OTP/OCE
Zhaohui Ye, PhD, CBER/OTP/OGT

Applicant Attendees:

David Altshuler, Executive Vice President, Global Research and Chief Scientific Officer
Morrey Atkinson, Executive Vice President, Chief Technical Operations Officer
Tony Boitano, Vice President, Stem Cell Research
Carmen Bozic, Executive Vice President, Chief Medical Officer
Ciaran Brady, Vice President, Manufacturing Technical Sciences
Sandy Dickin, Senior Director, Regulatory Strategy
Jean-Marc Guettier, Senior Vice President, Clinical Development
William Hobbs, Vice President, Clinical Pipeline Development
Laurie Kelliher, Executive Director, Regulatory Affairs

Stephanie Krogmeier, Vice President, Global Regulatory Affairs
Andrew Kuzmission, Vice President, Chemistry Manufacturing and Controls
Kimberly Moore, Vice President, Analytical Development
Juliana Muscat, Vice President, Operational Area Quality
Brett Richardson, Associate Director, Regulatory Strategy
Leorah Ross, Executive Medical Director, Global Patient Safety
Christopher Simard, Vice President, Patient Safety, Medical Safety and Risk Management
Nia Tatsis, Executive Vice President, Chief Regulatory and Quality Officer
Bo Yang, Vice President, Biometrics
Angela Yen, Senior Director, Computational Genomics

Agenda:

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

- None at this time

2. Information regarding major safety concerns.

- **Clinical:**

- Delayed platelet engraftment

- i. As compared to post allogeneic transplant platelet recovery

Meeting Discussion:

FDA informed the Applicant that 46 out of 54 patients achieved platelet engraftment past Day-30 which is longer as compared to the post allogeneic stem cell transplant platelet recovery.

Additionally, 4 of these 46 subjects achieved platelet engraftment between Days 60-100.

- ii. And despite the use of thrombopoietin (TPO) mimetics in some patients

Meeting Discussion:

FDA informed the Applicant that 5 out of 46 patients achieved engraftment after Day-100 despite the use of thrombopoietin (TPO) mimetics and remain thrombocytopenic up to month 24. In these subjects the main concern are low platelet counts, risk of bleeding events, need of transfusions and the follow up plan.

Applicant acknowledged the data summarized about delayed platelet engraftment and thrombocytopenia in study patients. Applicant stated that their data analysis showed similar results and mentioned the potential effect due to the presence of spleen on platelet recovery in autologous transplant patients treated with gene therapies. Applicant proposed to address this concern in the product label.

- **Chemistry, Manufacturing, and Controls (CMC):**

- Observation of visible foreign particulates in exa-cel drug product (DP) including the following:
 - a. How (b) (4) lot release appearance testing is performed, the ability to identify particulates in product (if present), when material is discarded and when deviations are opened
 - b. Plans and timelines for addressing the presence of visible foreign particulates during (b) (4) in the final vial product. Release of vials with visible particulates observed during 100% inspection does not align with expectations for injectable products.

Meeting Discussion:

FDA explained that the word “foreign” in our comments includes intrinsic and extrinsic visible particulates and any vials containing these particulates should be rejected. This requirement aligns with (b) (4) and the draft FDA guidance *Inspection of Injectable Products for Visible Particulates* (Dec 2021).

The Applicant proposed that inherent and intrinsic particles are deemed acceptable if present in the drug product below a certain level ((b) (4) vial) and have been assessed by health hazard assessments. Low levels of particulates are expected to be removed with the application of an 18µm filter at the point of patient administration.

FDA explained that particles, even if intrinsic to the manufacturing process and chemically inert, can cause damage to patients if injected. Thus, FDA does not agree with the Applicant’s proposal to release drug product vials with visible particulates.

The Applicant is working with the (b) (4) supplier to minimize particulates originating from the (b) (4) as they agree this should be decreased as much as possible.

FDA reiterated that it must work within the current regulation, and the vials containing visible particles cannot be released commercially. Any vial containing intrinsic or extrinsic visible particles must be discarded. FDA acknowledged the potential impact this may have on the manufacturing process and the ability to meet the required dose.

The Applicant agreed to take this under advisement and will look into a process that will control this at a tighter level and understood the concern.

FDA asked that the visual inspection SOP be updated to include the vial rejection requirements. The Applicant questioned how the clinical site filter is still relevant if the SOP is changed. FDA stated that because visual inspection is probabilistic by nature and cannot be relied upon to detect and remove all particulates, the filter is still recommended until the manufacturing process does not release visible particulates.

- c. Insufficient data demonstrating the ability of the 18 micron filtration step to remove the identified particulates at the clinical sites prior to infusion. The studies you provided with the 18 micron (b) (4) filter are insufficient to support the ability of filters used at the clinical sites to clear the specific particulates generated in exa-cel manufacturing.

Meeting Discussion:

The Applicant stated that their study has shown the (b) (4) filter's ability to remove (b) (4) particulates greater than 18 microns in diameter and questioned what additional detail FDA needs to support the removal of particles. FDA explained they need data obtained using the filters that are used at the clinical sites and particles that are representative of the particulates observed in the drug product.

The Applicant said the filters used in the previous study and the clinical filters are the same; even though the Applicant does not dictate the source of 18µm stainless steel blood filters used at clinical sites, the (b) (4) filter is the only one available. The Applicant said they will commit to additional studies using more representative particulates, but it may take time to design and generate the data. FDA requested that the Applicant submit the

study plan and timeline for completion as soon as possible. The applicant agreed to do so.

- Non-agreement on the (b) (4) in-process hold times

Meeting Discussion:

FDA informed the Applicant that they did not have data to support the proposed maximum in-process hold times for (b) (4) manufacturing. The Applicant was asked to revise the maximum hold times based on the hold times used during process validation with a reasonable buffer to accommodate manufacturing flexibility. The Applicant asked if they could support maximum hold times with data from additional lots. FDA agreed the Applicant could submit data from additional commercial representative lots to support in-process maximum hold times.

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.
 - Review is ongoing. The need for Risk Evaluation and Mitigation Strategy (REMS), PMR or PMC remains undetermined at this juncture.
4. Any information requests sent, and responses not received.

The Agency noted these responses were received by the Mid-cycle Teleconference with the Applicant.

- Bioinformatics IR #8
 - Sent 9/19/23 – Due 9/22/23 (Extension granted: Due 9/26/23): Follow-up to IR #7 for information of all 50 loci nominated from analysis
 - OBPV/Epidemiology
 - Sent 9/22/23 – Due 9/25/23: Revision of wording to "Delayed platelet engraftment" to maintain consistency across similar CBER products
5. Any new information requests to be communicated.
 - As the review continues, new information requests will be conveyed as needed. Forthcoming information requests:
 - CMC
 - Bioinformatics
 - Clinical - Safety
 6. Proposed date(s) for the Late-Cycle meeting (LCM).

- a. The LCM between the Applicant and the Review Committee is currently scheduled for December 18, 2023, from 11:00AM – 12:00PM (ET).
 - b. The Agency intends to send the LCM meeting materials to the Applicant no later than December 8, 2023 in advance of the Late-cycle meeting.
 - c. If these timelines change, the Agency will communicate the updates to the Applicant during the course of the review.
7. Updates regarding plans for the AC meeting.
 - There are no plans for an AC meeting for this BLA.
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.

The Agency noted that some of these milestone dates are Saturdays so there will be an effort to work a day ahead to accommodate the weekend.

Mid-cycle meeting with applicant:	September 28, 2023
Late-Cycle with applicant:	December 18, 2023
Communicate Anticipated PMRs:	February 3, 2024
Communicate Proposed Labeling:	February 29, 2024
Communicate Proposed PMR/PMC:	February 29, 2024
Action Due Date:	March 30, 2024