



Our STN: BLA 125846/0

**MID-CYCLE COMMUNICATION
SUMMARY**
June 2, 2025

Fondazione Telethon ETS
Attention: Mike Yefimenko (US Agent)

(b) (4)

Dear Mike Yefimenko:

Attached is a copy of the summary of your May 12, 2025, 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 BLA 125846/0 in your future submissions related to the subject product.

If you have any questions, please contact Cecilia Crowley at (240) 402-2810 or by email at Cecilia.Crowley@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 125846/0
Product Name: (Etuvetidigene autotemcel) Autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells (HSPC) transduced ex-vivo using a lentiviral vector encoding the human Wiskott-Aldrich syndrome (WAS) gene; WASKYRA.
Proposed Indication for Use: Treatment of patients aged 6 months and older with Wiskott-Aldrich Syndrome (WAS) who have a mutation in the WAS gene and for whom no suitable human leukocyte antigen (HLA)-matched related haematopoietic stem cell donor is available.
Applicant: Fondazione Telethon ETS
Meeting Date & Time: May 12, 2025, at 10:00 am – 10:30 am (ET)
Committee Chair: Laura DeMaster
RPM: Cecilia Crowley

FDA Attendees:

Rachael Anatol, PhD, CBER/OTP
Judith Badoo, CBER/OD
Rabia Ballica, PhD, CBER/OCBQ/DMPQ
Jessica Boehmer, MBA, CBER/OTP/ORMRR
Cecilia Crowley, CBER/OTP/ORMRR
Laura DeMaster, PhD, CBER/OTP/OGT
Cherie Fathy, MD, CBER/OTP/OCE/DCEGM
Denise Gavin, PhD, CBER/OTP/OGT
Jared Greenleaf, CBER/OCBQ/DMPQ
Kathleen Jones, PhD, CBER/OCBQ/DMPQ
Anna Kwilas, PhD, CBER/OTP/OGT
Stella Lee, PhD, CBER/OTP/OGT
Wei Liang, PhD, CBER/OTP
Mara Miller, MA, CBER/OTP/ORMRR
Renuka Miller, PhD, CBER/OTP/OGT
Gopa Raychaudhuri, PhD, CBER/OD
Teisha Rowland, PhD, CBER/OTP/OGT
Kimberly Schultz, PhD, CBER/OTP/OGT
Shalini Seetharaman, MS, CBER/OTP/ORMRR
Rosa Sherafat-Kazemzadeh, MD, CBER/OTP/OCE/DCEGM
Ekaterini Tsilou, MD, CBER/OTP/OCE/DCEGM
Nicole Verdun, MD, CBER/OTP
Zhaohui Ye, PhD, CBER/OTP/OGT

FTE Attendees (virtual):

Francesca Ferrua

(b) (4)

Federica Miotto

Michela Palmisano

Koen van Rossem

Sean Russell

EMA Attendees (virtual):

Alessandro Aiuti

Violaine Closson-Carella

Patrick Celis

Caoimhin Concannon

Jayne Crowe

Coralie Deligny

Marianne Delville

Marie-Therese Duffour

Monika Jarzabek

Solene Maitenaz

Nathalie Morgenstejn

Jean-Michel Race

Simona Teodosiu

Gabriela Ullio

Discussion Summary:

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

a. Chemistry, Manufacturing, and Controls:

1. We do not agree to the removal of all process-related impurities testing from the (b) (4) lot release specification. The data provided in the OS do not adequately demonstrate that all (b) (4) process related impurities are controlled during (b) (4) manufacturing or cleared during DP manufacturing.

Meeting Discussion for Agenda item 1:

FDA has completed assessment of the information submitted for (b) (4) process-related impurities and agrees that tests for (b) (4) can be removed from the (b) (4) lot release specification. However, your commercial lot release specification for (b) (4) should include tests for (b) (4) because these attributes are less well controlled and associated with specific safety considerations. FDA will send a follow-up IR with a request to provide the level of all (b) (4) impurities per (b) (4) (rather than per (b) (4)) for all lots used

during clinical development and to provide a revised (b) (4) specification including the aforementioned tests with proposed acceptance criteria. Additionally, documentation for the (b) (4) assay, including assay SOP and validation information, will be requested by IR. FTE acknowledged the FDA statements.

2. We do not agree that the (b) (4) sampling plan is appropriate for the microbiological safety tests (i.e. sterility, in vitro adventitious viral agents, and mycoplasma). Furthermore, we do not agree that the (b) (4) sample used for sterility testing is stored appropriately.

Meeting Discussion for Agenda 2:

FDA acknowledges that the sampling points for mycoplasma and IVAA will be (b) (4) step. FDA will send an IR requesting justification that the (b) (4) does not impact the ability to detect contamination.

As conveyed in the IRs dated March 14, 2025, and April 23, 2025, FDA stated that samples (b) (4) DP for sterility testing should not be stored in a (b) (4) prior to testing per (b) (4). FDA will send a follow-up IR requesting the applicant's plan for implementing appropriate storage of (b) (4) DP samples. FTE acknowledged FDA's position.

3. We do not agree that the transduction unit operations of the DP manufacturing process are adequately controlled. Specifically, the description of the manufacturing process, process controls, and batch record lack ranges for the amount of LVV added.

Meeting Discussion for Agenda 3:

FDA acknowledges the information on the addition of LVV during DP transduction unit operations provided by the applicant in response to the IR dated April 23, 2025. FDA stated transduction operations are typically controlled by an (b) (4) rather than an (b) (4), and that follow-up IRs will be sent to the applicant to ensure they have adequate control of the transduction operations during etu-cel manufacturing. FTE acknowledged the FDA's concern.

4. We do not agree that the DP sample used for sterility testing is stored appropriately.

Meeting Discussion for Agenda 4:

This item was discussed with Agenda item #2.

5. We do not yet agree that the WAS Protein (WASP) assay is adequately controlled for DP testing. The assay is not adequately validated to demonstrate applicable variability in assay parameters (e.g. intermediate

precision), and it is unclear if the controls in place enable comparison of WASP values between DP lots or over time to support stability studies.

Meeting Discussion for Agenda 5:

FDA acknowledges the applicant's proposal to test patient and (b) (4) samples to assess the intermediate precision of the DP WASP assay and submit the data by June 16, 2025. The approach and timeline are acceptable. FTE confirmed that the testing of patient material includes the (b) (4) aspect of the WASP assay.

6. We do not agree that the transduction efficiency assay is adequately validated for use because the proposed DP specification acceptance criterion is not fully covered by the validated range.

Meeting Discussion for Agenda 6:

FDA has reviewed the applicant's response to the IR dated April 23, 2025, indicating that the transduction efficiency (TE) (b) (4). While FDA understands that this is a limitation of the current assay, this will not be acceptable for licensure. Linearity, precision, and accuracy should be demonstrated across the full range of the assay, including above (b) (4) transduction efficiency. FDA stated that FTE should identify why the assay is (b) (4) and address the issue or an alternative test should be used for transduction efficiency. FTE stated that they understood and indicated that they will be discussing the transduction efficiency assay with their CDMO.

7. We do not agree that the stability data provided in the OS adequately support the established DP shelf life.

Meeting Discussion for Agenda 7:

After reviewing the applicant's response to the IR dated April 23, 2025, FDA recommended testing the available PPQ lot samples that were manufactured in 2020. The test results may demonstrate stability and therefore represent the additional DP data needed to support the proposed commercial shelf-life. FDA went on to state that if any result fails to demonstrate stability of DP at (b) (4) years, this will not detract from the proposed shelf-life. FTE acknowledged FDA's recommendation and agreed to test lots. FDA will be sending a follow-up IR requesting a timeline for submission of the additional stability data.

8. We do not agree that the extractables and leachables assessment of the etu-cel drug product is adequate.

Meeting Discussion for Agenda 8:

FDA is reviewing the applicant's proposal and has no additional comments at this time. No discussion of this topic.

2. Information regarding major safety concerns. Note: there must be a pro-active statement included during the telecon regarding major safety concerns.
 - a. At this time, we have not identified safety concerns for your BLA.

Meeting Discussion for Agenda item 2:

There was no discussion of this agenda item during the meeting.

3. Preliminary Review Committee thinking regarding a) risk management, b) the potential need for any post-marketing requirement(s) (PMRs), and/or safety-related PMCs, and c.) the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk.
 - a. Discussion of any potential PMRs and PMCs is underway.
 - b. We do not anticipate the need for a REMS.

Meeting Discussion for Agenda item 3:

There was no discussion of this agenda item during the meeting.

4. Any information requests sent, and responses not received.
 - a. CMC IR #15 due 5/5/25; informal tcon was held with FTE on 4/30/25. CMC team is willing to accept timeline proposals for responses to parts 1/2/3 of IR by 5/8/25 and IR responses to parts 4-21 due 5/9/25 in advance to the scheduled Mid-Cycle meeting.

Meeting Discussion for Agenda item 4a:

FTE submitted responses to IR #15 by email on 5/9/25 and formal submission was received on 5/15/25.

- b. DMPQ IR #16 re: process validation and/evaluation; due 5/16/25.

Meeting Discussion for Agenda item 4b:

FTE plans to submit IR #16 responses by email. Responses to IR #16 were received on 5/20/25.

5. Any new information requests to be communicated.
 - a. New IRs will be conveyed as submission review continues.

Meeting Discussion for Agenda item 5:

There was no discussion of this agenda item during the meeting.

6. Proposed dates for the Late-Cycle Meeting and the Late-Cycle Meeting Materials:
 - a. Late-Cycle Meeting Materials to FTE: June 16, 2025
 - b. Late-Cycle Meeting with (FTE): June 26, 2025, at 11am-12pm

Meeting Discussion for Agenda item 6:

There was no discussion of this agenda item during the meeting.

7. Updates regarding plans for the AC meeting, if appropriate.
 - a. There is no plan to hold an Advisory Committee meeting.

Meeting Discussion for Agenda item 7:

There was no discussion of this agenda item during the meeting.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.
 - a. Communicate anticipated PMRs: July 30, 2025
 - b. Communicate PMCs, and begin labeling negotiations: August 11, 2025
 - c. PDUFA Date: September 10, 2025

Meeting Discussion for Agenda item 8:

There was no discussion of this agenda item during the meeting. Mid-Cycle Communication Summary will be sent to FTE by June 11, 2025.

9. Provide status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval. Ensure notification of intent to inspect manufacturing facilities has been issued.
 - a. We have no issues to report on the status of inspections.

Meeting Discussion for Agenda item 9:

There was no discussion of this agenda item during the meeting.