



Our STN: BL 125846/0

BLA APPROVAL

December 9, 2025

Fondazione Telethon ETS
Attention: Mike Yefimenko
(b) (4)
[REDACTED]

Dear Mike Yefimenko:

Please refer to your Biologics License Application (BLA) received January 10, 2025, submitted under section 351(a) of the Public Health Service Act (PHS Act) for etuvetidigene autotemcel.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2378 to Fondazione Telethon ETS, Rome, Italy, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product etuvetidigene autotemcel, which is indicated for the treatment of pediatric patients aged 6 months and older and adults with Wiskott-Aldrich Syndrome (WAS) who have a mutation in the WAS gene for whom hematopoietic stem cell transplantation (HSCT) is appropriate and no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

The review of this product was associated with the following National Clinical Trial (NCT) numbers: NCT01515462 and NCT03837483.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture etuvetidigene autotemcel and the WAS lentiviral vector at (b) (4) located at (b) (4),
(b) (4)

You may label your product with the proprietary name WASKYRA and market it in (b) (4) bags formulated at a concentration between $1.9 - 11.4 \times 10^6$ CD34+

cells/mL in 1 – 8 bags, where each bag contains between 10 – 20mL. The minimum recommended dose is 7×10^6 CD34+ cells/kg.

ADVISORY COMMITTEE

We did not refer your application to the Cellular, Tissue, and Gene Therapies Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for etuvetidigene autotemcel shall be six months from the date of manufacture when stored at <-130°C. The date of manufacture shall be defined as the date of final formulation of drug product (DP). The dating period for the WAS lentiviral vector shall be (b) (4) when stored at (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of etuvetidigene autotemcel to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at <https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations>:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of WASKYRA or in the manufacturing facilities.

LABELING

We hereby approve the draft content of labeling including the Package Insert submitted and received via email on December 9, 2025, and the draft package and container labels submitted under amendment #29, dated November 21, 2025 and under amendment #32, dated December 5, 2025.

WAIVER OF HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the Package Insert submitted on December 9, 2025. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels identical to the package and container labels submitted on November 21, 2025 and December 5, 2025, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <https://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm333969.pdf>.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125846/0 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. In addition to the reporting requirements in 21 CFR 600.80, you must submit adverse experience reports for secondary malignancies as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports* at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports> and FDA's Adverse Event reporting System website at <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions>. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at <https://www.fda.gov/vaccines-blood-biologics/lot-release/lot-distribution-database-ldd>.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher (PRV), as provided under section 529 of the FDCA. This PRV has been assigned a tracking number, PRV BLA 125846/0. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, **“Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”**
- This PRV may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the PRV may be transferred, but each person to whom the PRV is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this PRV, you should refer to this letter as an official record of the voucher. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred.
- FDA may revoke the PRV if the rare pediatric disease product for which the PRV was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a PRV must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease PRV Program webpage available at
<https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm>.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and

effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) 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 section 505(k)(1) of the FDCA will not be sufficient to identify a serious risk of secondary malignancies after administration of etuvetidigene autotemcel.

We have also determined that such an analysis will not be sufficient to assess a serious risk of patient exposure to any unknown at this time leachables from the product-contact materials in the etuvetidigene autotemcel manufacturing process.

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, if your application is approved, we have determined that you will be required to conduct the studies described below:

1. A postmarketing, prospective, observational study to assess and characterize the risk of secondary malignancies and long-term safety following treatment with etuvetidigene autotemcel. This study will enroll 14 patients with Wiskott- Aldrich Syndrome (WAS) who received treatment with etuvetidigene autotemcel. The enrolled patients will be followed for 15 years after product administration.

We acknowledge the timetable you submitted on November 21, 2025, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 30, 2026

Study Completion Date: June 30, 2046

Final Report Submission: December 31, 2046

2. An adequate leachables safety assessment for the TLT003 drug product (DP) through its manufacturing process, storage, and in-use conditions. The assessment must include both elemental and organic leachables from the formulation, storage and in-use preparation product-contacting components appearing cumulatively in final DP. The leachables study can be conducted without active ingredient by

simulating the DP manufacturing process from the (b) (4) step through in-use preparation steps of the simulated DP. Such study should use maximal hold times and temperatures at respective manufacturing process steps to assess cumulative leachables in the DP from the (b) (4) through product freezing, shelf-life, storage, thawing, and in-use processing. A final study report and toxicological risk assessment should be provided.

We acknowledge the timetable you submitted on November 21, 2025, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 31, 2026

Study Completion Date: September 30, 2026

Final Report Submission: December 31, 2026

Please submit the protocols to your IND 18919, with a cross-reference letter to this BLA, STN BL 125846 explaining that these protocols were submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA, STN BL 125846. For administrative purposes, all submissions related to these postmarketing studies required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**
- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm>.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letters of November 17, 2025, and December 4, 2025 as outlined below:

3. Fondazione Telethon ETS commits to implement and validate an assay measuring (b) (4). The final validation study report will be submitted as a “Postmarketing Commitment – Final Study Report” by December 31, 2026.

Final Report Submission: December 31, 2026

4. Fondazione Telethon ETS commits to implement and validate a drug product (DP) assay measuring (b) (4)

. The final report will be submitted as a “Postmarketing Commitment – Final Study Report” by December 31, 2026.

Final Report Submission: December 31, 2026

5. Fondazione Telethon ETS commits to perform a (b) (4)

under the intended conditions as described in BLA 125846. The final report will be submitted as a “Postmarketing Commitment – Final Study Report” by May 31, 2026.

Final Report Submission: May 31, 2026

6. Fondazione Telethon ETS commits to re-validate the (b) (4) assay to include the range of the commercial lot release criterion or implement and validate an alternative assay. The final validation study report will be submitted as a “Postmarketing Commitment – Final Study Report” by December 31, 2026.

Final Report Submission: December 31, 2026

7. Fondazione Telethon ETS commits to validate the updated (b) (4) test and reassess the criteria for drug product lot release. The final report will be submitted as a “Postmarketing Commitment – Final Study Report” by December 31, 2025.

Final Report Submission: December 31, 2025

8. Fondazione Telethon ETS commits to validate the following assays for robustness: (b) (4)

The final study reports will be submitted as a “Postmarketing Commitment - Final Study Report” by March 31, 2026.

Final Report Submission: March 31, 2026

9. Fondazione Telethon ETS commits to conduct a study measuring (b) (4). The final study report will be submitted as a “Postmarketing Commitment - Final Study Report” by September 30, 2026.

Final Report Submission: September 30, 2026

10. Fondazione Telethon ETS commits to perform additional (b) (4)

The final report will be submitted as a “Postmarketing Commitment – Final Study Report” by March 31, 2026.

Final Report Submission: March 31, 2026

11. Fondazione Telethon ETS commits to perform a study assessing the impact of the (b) (4)

LVV release. The final study report will be submitted as a “Postmarketing Commitment – Final Study Report” by May 31, 2026.

Final Report Submission: May 31, 2026

12. Fondazione Telethon ETS commits to perform an additional in-use DP stability study that includes an administration set equipped with a filter and assesses the viability of DP under the administration conditions described in the BLA. The final study report will be submitted as a “Postmarketing Commitment – Final Study Report” by November 30, 2026.

Final Report Submission: November 30, 2026

13. Fondazione Telethon ETS commits to perform a comparability study as part of the WASKYRA drug product (b) (4) assay as required by 21 CFR 610.9. The final validation study report will be submitted as a “Postmarketing Commitment - Final Study Report” by September 30, 2026.

Final Report Submission: September 30, 2026

14. Fondazione Telethon ETS commits to conduct an additional (b) (4) validation and to provide the validation study report to the Agency as a “Postmarketing Commitment – Final Study Report” by May 31, 2026.

Final Report Submission: May 31, 2026

15. Fondazione Telethon ETS commits to conduct an additional (b) (4) validation for the (b) (4) and to provide the validation study report to the Agency as a “Postmarketing Commitment – Final Study Report” by April 30, 2026.

Final Report Submission: April 30, 2026

16. Fondazione Telethon ETS commits to conducting an additional CCIT method validation to be used following shipping of the final container (b) (4) Freezing Bags) and to provide both the method validation study report to the Agency as a “Post-marketing Commitment – Final Study Report” by April 30, 2026.

Final Report Submission: April 30, 2026

17. Fondazione Telethon ETS commits to conduct an additional CCIT validation for the final product container closure system and to provide the validation study report to the Agency as a “Postmarketing Commitment – Final Study Report” by September 30, 2026.

Final Report Submission: September 30, 2026

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125846. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Melissa Mendoza, JD
Director
Office of Compliance and Biologics Quality
Center for Biologics
Evaluation and Research

Megha Kaushal, MD
Acting Deputy Director
Office of Therapeutic Products
Center for Biologics
Evaluation and Research

