Summary Basis for Regulatory Action

Date:	**December 9, 2025**
From:	Laura DeMaster, PhD Review Committee Chair Office of Gene Therapy (OGT) Office of Therapeutic Products (OTP)
BLA STN:	**125846**
Applicant:	**Fondazione Telethon ETS**
Submission Receipt Date:	January 10, 2025
Action Due Date:	December 10, 2025
Proper Name:	etuvetidigene autotemcel
Proprietary Name:	**WASKYRA**
Indication:	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.

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of etuvetidigene autotemcel via traditional approval pathway.

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Director, Product Office

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
Regulatory	Cecilia Crowley, CBER/OTP/ORMRR
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC and Product Office)	Laura DeMaster, CBER/OTP/OGT Jared Greenleaf, CBER/OCBQ/DMPQ George Kastanis, CBER/OCBQ/DBSQC Stella Lee, CBER/OTP/OGT Tao Pan, CBER/OCBQ/DBSQC/LAC Teisha Rowland, CBER/OTP/OGT Wei Tu, CBER/OCBQ/DBSQC/LBVI Debra Vause, CBER/OCBQ/DMPQ Claire Wernly, CBER/OCBQ/DBSQC/LMIVTS
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Gumei Liu, CBER/OTP/PSPS Rochelle DalsanVaughn, CBER/OBPV/DPV Jennifer Chan, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Freda Cooner, CBER/OBPV/DB Jiang (Jessica) Hu, CBER/OBPV/DB
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1. Introduction

Fondazione Telethon ETS, (herein Applicant or FTE) submitted a Biologics License Application (BLA), STN 125846, for licensure of etuvetidigene autotemcel (etu-cel or Telethon-003, TLT003) with the proprietary name of WASKYRA. WASKYRA is an autologous hematopoietic stem cell-based gene therapy 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 clinical program for WASKYRA included two open-label, single-arm studies (TIGET-WAS and OTL-103-4) and two Expanded Access Program (EAP) studies, providing substantive evidence of effectiveness and safety from pooled data of 27 pediatric and adult male patients with severe WAS.

The primary efficacy endpoints demonstrated significant clinical improvements in both severe infection and moderate to severe bleeding rates following WASKYRA treatment. Severe infections decreased from 2.00 infections per person-year of observation (PYO) in the 12 months before treatment to 0.16 infections per PYO in the 6–18-month period post-treatment, with 70.4% of patients experiencing severe infections pre-treatment compared to only 34.6% post-treatment. Similarly, moderate and severe bleeding events decreased from 2.00 events per PYO pre-treatment to 0.80 events per PYO in the first 12 months post-treatment, with even greater reductions observed in long-term follow-up (0.03 events per PYO in the >4-year period). These improvements occurred despite normalization of social interactions, discontinuation of immunoglobulin replacement therapy and reduction of sustained antimicrobial treatment in most patients, indicating restoration of immune function.

The safety evaluation revealed an acceptable risk profile. All patients experienced at least one adverse event (AE) during the study period. A total of 67 serious adverse events (SAEs) were reported in 22 patients (81.5%), with the majority occurring within the first 6 months post-treatment during the period of immune reconstitution. One death occurred in an adult patient in EAP. None of the adverse events were considered related to WASKYRA. No evidence of insertional oncogenesis or abnormal clonal proliferation was observed during the study period. The overall benefit-risk profile for WASKYRA is favorable.

Given the theoretical long-term risks associated with lentiviral gene therapy and the relatively small safety database, a comprehensive, 15-year observational study of 14 patients has been established as a postmarketing requirement (PMR) to monitor for long-term safety outcomes, particularly focusing on the potential development of secondary malignancies and other delayed adverse effects.

WASKYRA received Orphan Drug, Rare Pediatric Disease, Priority Review and Regenerative Medicine Advanced Therapy designations. Upon BLA approval, the FDA awarded FTE a Rare Pediatric Disease Priority Review Voucher.

Regulatory Flexibility

The FDA employed a comprehensive and flexible approach to review the application, collaborating closely with the applicant and providing feedback in real-time throughout the process. This included assembling cross-functional review teams that included product quality and clinical expertise to ensure a thorough evaluation from multiple perspectives. During the review of WASKYRA, the FDA exercised regulatory flexibility across four critical areas: rare disease considerations, clinical trial design, mechanism of action, and chemistry, manufacturing and controls (CMC).

A. Clinical

The rare disease context of WAS encompassed both the small patient population and the significant unmet medical need in patients lacking suitable HLA-matched donors for conventional HSCT. The FDA accepted open-label, single-arm studies and incorporated real-world data from the EAP, to provide substantive evidence of effectiveness. The gene therapy's direct targeting of the underlying genetic defect in *WAS* provides critical mechanistic support for the observed clinical benefits. This regulatory flexibility enabled access to a therapeutic option that demonstrated robust and sustained clinical improvements with an acceptable safety profile in patients with this life-threatening rare disease.

B. CMC

Considering the clinical benefit observed in the clinical study and to enable approval and timely access to the product, FDA exercised regulatory flexibility to balance pre- and post-approval expectations for CMC data. FDA exerted CMC regulatory flexibility regarding potency assurance and analytical method validation. Specifically, FDA permitted a potency assurance strategy based on WASP expression assay and an interim analysis demonstrating correlation of WASP expression values in the final product with increases in platelet count between baseline and Day 180, a relevant clinical outcome, rather than a drug product (DP) functional potency assay. As discussed in Section 3, two PMCs were issued related to potency assurance.

Additionally, FDA allowed the Applicant to utilize data from a similar genetically modified CD34+ cell product to support analytical method validations based on the justification that it is sufficiently representative of WASKYRA for these purposes. In addition to the specific flexibilities listed here, additional information that is necessary to ensure long-term product quality, but for which its absence does not pose risks that should delay product availability, will be provided through post marketing requirements (PMRs) and post marketing commitments (PMCs) summarized in Section 3.

2. Background

Wiskott-Aldrich syndrome is an X-linked recessive primary immunodeficiency disorder caused by mutations in the WAS gene located on chromosome Xp11.23. The WAS gene encodes the Wiskott-Aldrich syndrome protein (WASP), which plays a crucial role in actin cytoskeleton reorganization and is essential for proper immune cell function, particularly in T cells, B cells, and platelets. Mutations in this gene result in defective or

absent WASP expression, leading to impaired cell motility, defective immunological synapse formation, and abnormal platelet development and function.

WAS affects approximately 1-10 per million live male births and presents with a classic triad of thrombocytopenia with small platelets, eczema, and recurrent infections. The clinical severity varies based on the type of WAS mutation, ranging from classic severe WAS to milder variants like X-linked thrombocytopenia (XLT). Patients typically present in infancy with bleeding episodes due to thrombocytopenia, followed by the development of eczematous skin lesions and increased susceptibility to bacterial, viral, and opportunistic infections. Without treatment, patients face significant morbidity from bleeding complications, severe infections, autoimmune disorders, and an increased risk of malignancies, particularly lymphomas, with historically poor long-term survival.

Current treatment approaches for WAS focus on supportive care and Hematopoietic stem cell transplantation (HSCT). Supportive management includes platelet transfusions for severe bleeding, immunoglobulin replacement therapy, prophylactic antibiotics, and aggressive treatment of infections. Thrombopoietin receptor agonists (TPO-RAs) such as eltrombopag and romiplostim are increasingly used off-label to help manage thrombocytopenia in patients with WAS, though their efficacy may be limited due to the underlying platelet dysfunction. HSCT remains the current standard of care treatment, with best outcomes achieved when performed early in life with HLA-matched sibling donors. Gene therapy has emerged as a promising alternative for patients lacking suitable donors, with several clinical trials demonstrating successful restoration of WASP expression and immune function. Additional supportive measures include splenectomy in select cases to improve platelet counts, though this increases infection risk and requires careful consideration of timing and patient selection.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Orphan Drug designation granted	March 9, 2010
2. Pre-IND meeting	May 5, 2017
3. Rare Pediatric Disease designation granted	December 1, 2017
4. IND submission (IND 18919)	May 15, 2019
5. Regenerative Medicine Advanced Therapy designation granted	July 11, 2019
6. Pre-BLA meeting	November 15, 2024
7. BLA 125846/0 submission	January 10, 2025
8. BLA filed	March 10, 2025
9. Mid-Cycle communication	May 12, 2025
10. Late-Cycle meeting	June 26, 2025
11. Major Amendment	August 5, 2025
12. Action Due Date	December 10, 2025

3. Chemistry Manufacturing and Controls (CMC)

This BLA includes an adequate description of the manufacturing process and testing of WASKYRA. The FDA CMC review team concludes that the manufacturing process,

along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics.

a. Product Quality

Manufacturing Summary

To manufacture WASKYRA, autologous hematopoietic stem and progenitor cells (HSPCs) are collected from each patient at a Qualified Treatment Center (QTC), following HSPC mobilization with granulocyte-colony stimulating factor (G-CSF) and plerixafor. The apheresis material is shipped to AGC Biologics (Bresso, Milan, Italy) for drug substance (DS)/DP manufacturing. Briefly, the apheresis material is enriched for cells expressing CD34 by (b) (4) The washed, transduced cells are then formulated in cryopreservation solution (5% v/v DMSO, 7% w/v HSA in 0.9% w/v sodium chloride) at a target concentration of 2 – 11.4 x 10^6 total viable cells/mL (1.9 – 11.4E6 CD34+ cells/mL) and filled into (b) (4) ethylene vinyl acetate (EVA) bag(s). The formulated DP is filled into one to eight bags, each containing 10 to 20 mL of WASKYRA depending on the number of cells produced. Bags are cryopreserved at ≤ -130°C in vapor-phase liquid nitrogen and shipped in a liquid nitrogen dry shipper to the QTC for administration back to the same patient. WASKYRA bags remain in cryostorage until immediately prior to infusion.

WASKYRA is composed of an autologous CD34+ enriched cell population that contains HSPCs transduced ex vivo using a nonreplicating, self-inactivated LVV (WAS LVV) that encodes the WAS gene and is based on HIV-1 and (b) (4) LVV release and stability testing ensure quality prior to introduction into the DP manufacturing process.

Manufacturing Control Strategy

The WASKYRA manufacturing control strategy consists of (1) raw material, component, and reagent qualification programs; (2) in-process monitoring; (3) in-process control testing; (4) lot release and stability testing; (5) manufacturing process validation and continuous process verification; and (6) traceability through chain of identity and chain of custody (COI/COC). The raw material, component and reagent qualification program consists of source material risk assessment,

vendor qualification, confirmation of the certificate of analysis, and material testing. Raw materials derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents. Critical process parameters are established for unit operations based on process knowledge and risk assessment studies. In-process monitoring and controls are implemented throughout the process to support process consistency. Lot release test methods are suitably validated or verified. The suitability of the commercial WASKYRA manufacturing process was assessed at AGC Biologic's Bresso manufacturing facility using (b) (4) -derived starting material. Process validation studies demonstrated control of the manufacturing process. Additional validation studies, including aseptic process simulation and shipping validation studies, were also performed. The WAS LVV manufacturing process was also validated. WASKYRA specifications are adequate to ensure product quality and consistency with DP used in the clinical study. COI/COC are established at the time of apheresis collection and maintained throughout the manufacturing process to administration to ensure that patient receives the correct autologous lot.

Comparability Assessments

During the review of the BLA, the comparability of products manufactured at different manufacturing facilities was assessed to enable pooling of clinical data. Two AGC Biologics manufacturing facilities were used to manufacture clinical DP. Both facilities were able to produce comparable products. Additional manufacturing process changes were implemented during product development, including changes in (b) (4) and transitioning from a fresh to a cryopreserved formulation for the final DP. Overall (b) (4) different DP manufacturing process versions were used during the clinical program. While comparability was not directly assessed across all manufacturing process versions, adequate data on DP quality attributes were provided to support clinical assessment of patient data.

Manufacturing Risks, Potential Safety Concerns, and Management

Product Mix-Up

WASKYRA is an autologous product manufactured in a multi-product manufacturing facility; as such, product mix-ups, either of autologous lots or with other stem cell products manufactured at the same facility, would result in potential risks. COI/COC is established at the point of apheresis collection and checked throughout the manufacturing process to ensure that the patient receives the correct autologous lot. COI/COC is maintained through barcodes and human-readable identifiers present on labels. Additionally, (b) (4) manufactured in a production suite at any given time. Patient identifiers are also confirmed prior to administration. Lot release testing confirms product identity.

Replication Competent Lentivirus (RCL)

RCL is a theoretical concern for the WASKYRA manufacturing process. The likelihood of RCL generation is reduced by the WAS LVV design: (b) (4)

(b) (4)

In accordance with current FDA guidance the final WAS LVV and production cells are tested by co-culture prior to release and use in the WASKYRA manufacturing process.

Insertional Oncogenesis

While LVV integration poses a risk for insertional mutagenesis, no risk-associated integration profiles have been observed to date for WASKYRA. The risk of insertional oncogenesis is theoretically reduced through WASKYRA lot release testing acceptance criteria, with a maximum upper limit for vector copy number (VCN) integrations. The upper VCN limit is supported by lots administered during clinical trials.

CMC PMCs/PMR

The following issues were identified but could not be resolved during the BLA review cycle. To allow patient access, the issues will be resolved through a post marketing requirement (PMR) and postmarketing commitments (PMCs) by December 31, 2026.

Two issues related to process-related impurities in DP were unresolved: 1) the leachables analysis did not include the contribution of major process components utilized in WASKYRA manufacturing, and 2) no empirical data were provided to demonstrate the reduction of LVV impurities in the DP manufacturing process. To resolve the leachables issue, an additional study will be performed to evaluate the cumulative leachables profile in the DP and update the toxicological risk assessment as a PMR. FTE will also conduct a study to assess clearance of LVV process-related impurities from the DP as a PMC.

As the potency assurance strategy for commercial etu-cel is based on WASP expression lot release criteria and the correlation of WASP expression values in DP with a relevant clinical outcome, FTE agreed to two PMCs related to potency assurance: 1) FTE will implement and validate an assay measuring (b) (4) WASP expressed by (b) (4) , and 2) FTE will either implement and validate a DP assay measuring (b) (4) measured for DP lot release and the specific correlating clinical parameter used to establish the potency assurance strategy for licensure.

While the submission included information on the stability of (b) (4) additional data are needed to support the shelf-life of (b) (4) used for WASKYRA manufacturing. FTE committed to perform a (b) (4) .

The following issues related to WAS LVV were unresolved and will be addressed as PMCs. FTE will perform 1) a study assessing the impact of the (b) (4) LVV, and 2) additional (b) (4)

Several assays were not adequately validated, and FTE committed to additional studies accordingly:

- The validation study for the (b) (4) assay does not adequately evaluate the upper end of the assay range to support the commercial DP lot release acceptance criterion. FTE will either re-validate the (b) (4) assay to include the entire range of the lot release criterion or implement and validate an alternative assay measuring this attribute.
- The (b) (4) test has not been adequately validated to support the lot release acceptance criteria. Data on DP (b) (4) was not collected during the clinical study, and the commercial release criteria for (b) (4) is based on the (b) (4) . FTE will perform additional assay validation and reassess the (b) (4) acceptance criteria as a PMC.
- The (b) (4) assays and the (b) (4) assay were not adequately validated for robustness.

While post-thaw DP data were provided to demonstrate post-thaw stability of WASKYRA, the in-use stability study did not include the administration set filter. To resolve this issue, FTE committed to perform an additional in-use stability study to assess DP viability under the administration conditions described in the BLA.

b. Testing Specifications

The final WAKYRA lot release specification is shown in Table 1. The analytical methods and their validations and/or qualifications reviewed for the WASKYRA drug substance(s) and/or drug product were found to be adequate for the intended use, except for the outstanding issue for testing mycoplasma of drug product. FTE has provided written commitment to resolve the issue as a PMC.

Table 1: Final Commercial WASKYRA Release Specification

Attribute Category	Test	Method	Acceptance Criteria
General	Viable cell concentration	(b) (4)	2.0 – 11.4 x 10^6 cells/mL
General	Appearance	Visual assessment (b) (4)	A cloudy to clear, colourless to yellow or pink dispersion of cells
Identity / Purity	Immunophenotype ($CD34^+$)	(b) (4)	
Identity / Potency	WASP/Transgene Expression (b) (4)	(b) (4)	
Potency / Purity	Viability	(b) (4)	
Potency / Safety	Vector Copy Number (VCN)	(b) (4)	
Potency / Safety	Vector Copy Number (b) (4)	(b) (4)	
Potency	Transduction Efficiency	(b) (4)	
Potency	(b) (4)		
Potency	(b) (4)		
Potency	(b) (4)		
Safety	Sterility	(b) (4)	No growth
Safety	Bacterial Endotoxins	(b) (4)	
Safety	Mycoplasma	(b) (4)	Not detectable

c. CBER Lot Release

CBER Lot Release, including the submission of product samples to CBER, is not required. The basis for this decision is that WASKYRA is an autologous product; as such each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of WASKYRA is listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Location	Activity	Most Recent Inspection
Facility: AGC Biologics S.p.A., Via Meucci 3, 20091 Bresso, Milan, Italy FEI#: 3020270660	• LVV/DS/DP (cell therapy product) manufacture/storage LVV release testing • (b) (4) /DP QC and release testing (microbiological, sterility, and biological assays) • Primary and secondary packaging	CBER/DMPQ PLI (b) (4) November 2023 VAI

CBER – Center for Biologics Evaluation and Research; DMPQ: Division of Manufacturing and Product Quality; DS – drug substance; DP – drug product; QC – quality control; VAI – Voluntary Action Indicated; PLI – Pre-License Inspection; LVV – Lentiviral vector

A PLI of AGC Biologics S.p.A. was conducted by CBER from November 8 – 20, 2023. All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

WASKYRA DP is filled into a 50 mL (b) (4) Freezing Bag (i.e., a cryobag) manufactured by (b) (4) . The material of construction of the cryobag is ethylene vinyl acetate (EVA) film. The bag is 510(k) cleared (No. (b) (4)). Each primary cryobag is sealed, labelled, and packaged into an overwrap EVA bag which is also sealed; the packaged DP is then cryopreserved. The bags are intended for a single freeze-thaw cycle. The cryobags are frozen using a (b) (4) process and stored and shipped in liquid nitrogen at <-130°C.

(b) (4) performed container closure integrity testing at their facility located in (b) (4) , employing the (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

I. Nonclinical Pharmacology/Toxicology

In vitro pharmacology studies demonstrated that analogous (b) (4) -grade WAS LVV transduced CD34+ HSPCs derived from WAS patients corrected T cell, B cell, and

dendritic cell (DC) function. In vivo murine pharmacology studies using surrogate lineage negative (Lin-) bone marrow (BM) cells transduced with WAS LVV transferred into WAS-deficient mice increased B cell, platelet, and granulocyte cells and corrected T cell, B cell, and DC function. This also resulted in reduced autoantibodies and gastrointestinal colitis normally observed in WAS-deficient mice.

In vivo pharmacokinetic studies were conducted using CD34+ HSPCs from healthy donors transduced with WAS LVV and infused into severely immunodeficient mice. The transplanted human HSPCs differentiated into both lymphoid and myeloid lineages in various hematopoietic organs. WAS LVV biodistribution was limited to the hematopoietic compartment with no evidence of bystander transduction in non-hematopoietic cells or germline transmission and no evidence of vector integration in murine cells. Gene integration analysis showed diverse insertion patterns without clustering near oncogenes or tumor suppressor genes.

In vivo long-term engraftment in primary or secondary WAS-deficient gene therapy (GT) bone marrow transplant (BMT) recipient mice that received Lin- murine BM cells transduced with the WAS LVV showed no adverse findings in survival. Tumors were either of non-hematopoietic origin or lymphomas were of host origin and showed no evidence of LVV integration.

No carcinogenicity, developmental and reproductive toxicology (DART) studies, and safety pharmacology studies were conducted for WASKYRA. These studies are not warranted based on the drug product characteristics and safety profile.

II. Clinical Pharmacology

The clinical pharmacology assessment of WASKYRA included two open-label, single-arm studies (Studies TIGET-WAS and OTL-103-4).

Pharmacokinetics of WASKYRA
Given the product characteristics of WASKYRA, conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

Pharmacodynamics of WASKYRA
WASKYRA is an autologous CD34+ HSPC cell population, transduced ex vivo using an LVV encoding the human WAS gene. When infused into the participant following the administration of a reduced intensity conditioning (RIC) regimen, the genetically corrected cells engraft and repopulate the hematopoietic compartment, giving rise to biologically active lymphoid and myeloid lineages expressing functional WASP.

The engraftment of gene-corrected cells and WASP gene expression were evaluated as with following pharmacodynamic biomarkers as secondary efficacy endpoints: genetically corrected cell engraftment (as evaluated by vector copy number [VCN]/cell, equivalent to percentage of gene-marked cells assuming a VCN of 1), WASP expression (in all peripheral blood [PB] cell types), T-cell function (represented by counts per minute and stimulation index), and platelet count.

Adequate engraftment of gene-modified cells was observed in all participants, with a median time to engraftment of 32 days (as determined by the percentage of gene-corrected cells). This engraftment was multilineage, affecting both BM and PB cell populations, and was maintained in evaluable participants for up to 8 years post-treatment.

WASP expression increased in all PB cell types (platelets, lymphocytes, B cells, T cells, natural killer cells, and monocytes) after WASKYRA treatment. The median percentage of PB cells expressing WASP remained relatively stable from Day 180 to the final analyzed timepoint at Year 8, demonstrating sustained transgene expression.

Dose evaluation
A range of doses were studied in clinical studies of WASKYRA based on the number of HSPCs harvested for transduction for each patient. Based on the results of gene-corrected cell engraftment, T-cell function, and WASP expression, there is no evidence of correlation between WASKYRA cell dose and these responses.

Immunogenicity
No anti-WASP antibodies have been detected in any of the 27 participants treated with WASKYRA, and no events indicative of immunogenicity have been reported.

III. Clinical/Statistical

a. Clinical Program

The clinical program of WASKYRA includes two open-label, single-arm studies (Studies TIGET-WAS and OTL-103-4) and two studies in an Expanded Access Program (EAP; Studies 205030, Hospital Exemption [HE], and 206257, Compassionate Use Program [CUP]). Substantial evidence of effectiveness and safety is demonstrated by pooled data from 27 patients treated in the studies.

All patients were male and the majority (20/27 [74.1%]) were White. Age at the time of WASKYRA treatment ranged from 0.98 to 35.1 years, with 11 patients <24 months, 11 patients ≥24 months to 11 years, and 5 patients >11 years of age. Patients were classified as having severe WAS based on at least one of three criteria: a Zhu clinical score ≥3.0, a severe *WAS* mutation, or absent Wiskott-Aldrich syndrome protein (WASP) expression. The Zhu score, a five-point scale assessing disease severity, considers factors such as thrombocytopenia, eczema, immunodeficiency, infections, autoimmunity, and malignancies. Severe *WAS* mutations typically included nonsense mutations, deletions, and insertions resulting in absent WASP expression or truncated WASP. Absent WASP expression was defined as <5% of lymphocytes expressing WASP. In the study population, 25 out of 27 patients (92%) had a Zhu score ≥3.0 at baseline, indicating severe clinical disease. Additionally, 22 out of 27 (81%) patients were identified as having severe WAS mutations. It is noteworthy that WAS presents as a continuum of dysfunction from mild to severe, reflecting various degrees of WASP deficiency or loss of function.

The primary efficacy endpoints for the integrated analysis of WASKYRA in treating WAS were: (i) overall survival, (ii) the rate of severe infections from 6 to 18 months post-

treatment compared to the 12 months before treatment, and (iii) the rate of moderate and severe bleeding events in the first 12 months post-treatment compared to the 12 months before treatment.

Overall Survival

The proportion of patients surviving at the end of follow-up was 96% (95% CI: 82, 99). The median duration of patient follow-up in all surviving patients was 5.72 years ranging from 1.19 to 13.26 years. Overall survival rates of patients in Studies TIGET-WAS and OTL-103-4 were both 100% at last follow up. A systematic literature review[1] submitted in the BLA reported 1-year OS rate of 92.2% and 5-year OS rate of 74-92% in patients with WAS who received HSCT compared to 1-year and 5-year OS rates of 96% after WASKYRA treatment.

Interpretation of OS data is challenging. The single-arm study design lacks a contemporaneous control group; therefore, direct comparisons to the historical HSCT outcomes could potentially be confounded by differences in patient selection, conditioning regimen, supportive care advances, and treatment era effects. The small sample size (n=27) limits statistical power for detecting rare but serious AEs, and the highly selected patient population treated at specialized centers may not reflect outcomes achievable in broader clinical practice. Despite these limitations, the consistent survival benefit observed across different studies (TIGET-WAS: 100%, OTL-103-4: 100%, EAP: 89%), combined with the absence of graft versus host disease and reduced conditioning intensity compared to HSCT, provides compelling evidence that WASKYRA offers a favorable risk-benefit profile with excellent survival outcomes for patients with severe WAS who lack suitable donors or are at high risk for transplant-related complications.

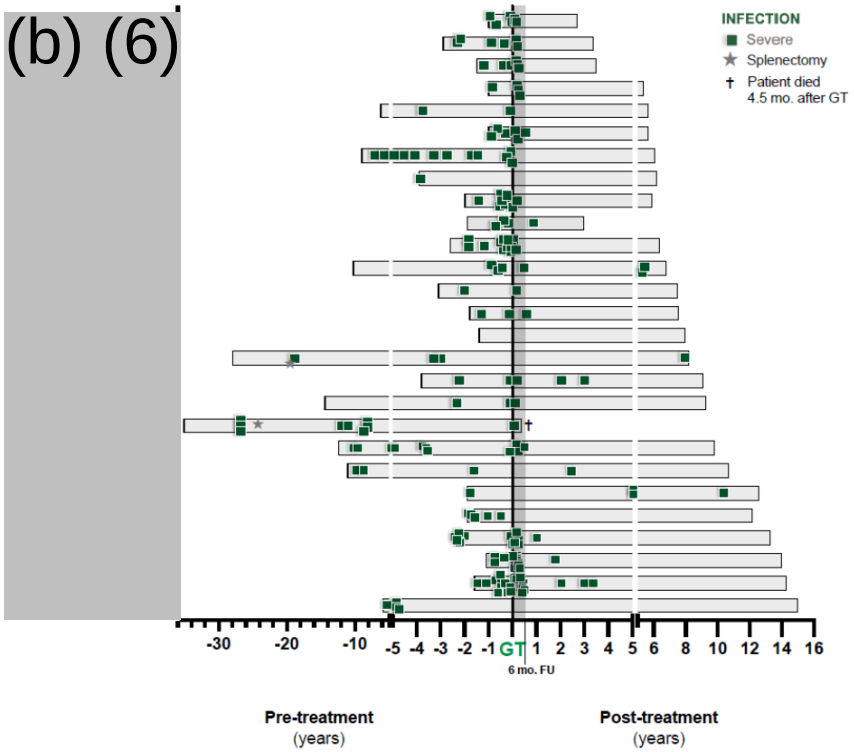
Severe Infections

The analysis of severe infections in patients treated with WASKYRA demonstrated a nominally significant reduction in infection rates following treatment. Severe infections, defined as "Infections and infestations" at Common Terminology Criteria for Adverse Events (CTCAE v5.0) Grade 3 or above, were primarily compared between the 12-month period before GT and the 6 to 18-month period post treatment. The rate of severe infections decreased from 2.00 (95% CI: 1.50-2.61) infections per person-year of observation (PYO) in the 12 months before GT, to 0.16 (95% CI: 0.04-0.40) infections per PYO in the 6 to 18-month period post-treatment. In the 12 months before GT, 19 (70.4%) patients experienced severe infections, with 54 total events recorded. This contrasts with the >6 months follow-up period post-treatment, where only 9 (34.6%) patients experienced severe infections, with 14 total events recorded. The most frequent severe infections were device-related infections, pneumonia, cytomegalovirus infections, and cellulitis. There was an increase in the rate of severe infections in the first 6 months following WASKYRA infusion (3.15 infections per PYO). This was attributed to the patients' increased vulnerability during immune system reconstitution after conditioning.

[1] Albert MH, Slatter MA, Gennery AR, et al. Hematopoietic stem cell transplantation for Wiskott-Aldrich syndrome: an EBMT Inborn Errors Working Party analysis. Blood. 2022;139(13):2066-2079. doi:10.1182/blood.2021014687

However, the infection rate significantly decreased after this initial period and remained low throughout the study. The reduction in severe infection rates was consistent across different studies within the WASKYRA program, indicating comparable treatment effects between fresh and cryopreserved formulations of Telethon-003. This improvement in infection rates occurred in conjunction with (i) normalization of patients' social interactions and (ii) discontinuation of immunoglobulin replacement therapy (IgRT) and sustained antimicrobial treatment in 23 (92.0%) patients who received IgRT post-WASKYRA.

Figure1. Severe Infections Over Time in WASKYRA-Treated Patients



Source: Module 2.5 Clinical Overview Addendum
Abbreviations: FU, follow-up; GT, gene therapy

Moderate and Severe Bleeding Events

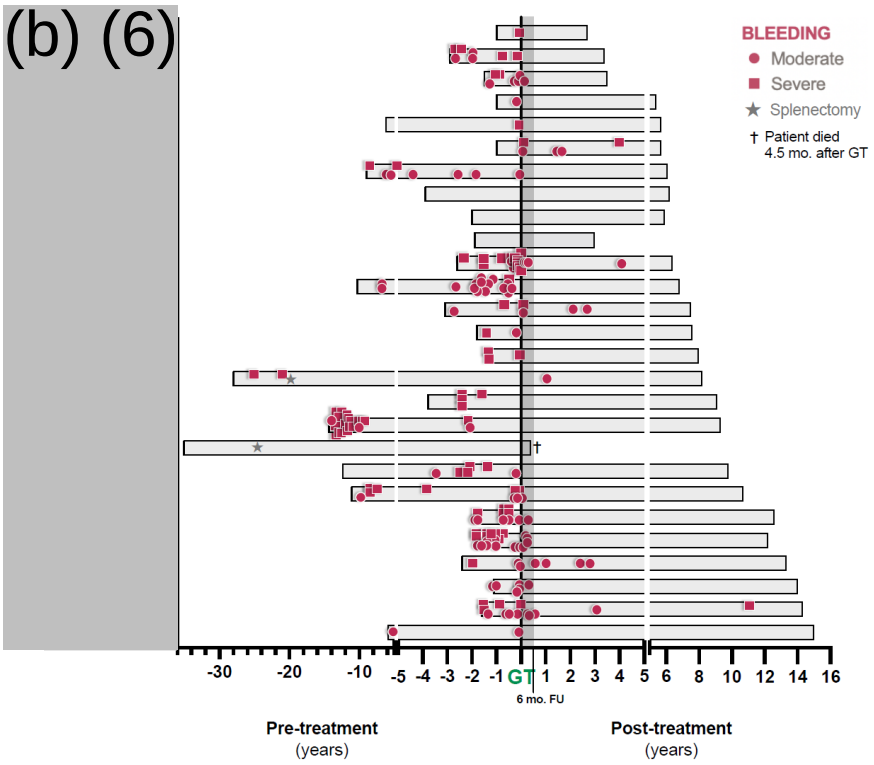
The analysis of moderate and severe bleeding events in patients treated with WASKYRA for WAS revealed a nominally significant reduction in bleeding episodes following GT. Bleeding events were identified using a Customized Query based on MedDRA version 26.0 Hemorrhage (excluding Laboratory Terms), Standardized MedDRA Query (SMQ) (Narrow). The primary comparison was between the 12-month period before GT and the 12-month period post-treatment; additional long-term follow-up data were also analyzed.

The rate of moderate and severe bleeding events decreased from 2.00 (95% CI: 1.50-2.61) events per PYO in the 12 months before GT to 0.80 (95% CI: 0.49-1.22) events per PYO in the 12 months following WASKYRA infusion. This reduction was even more pronounced in the long-term follow-up, with the rate decreasing to 0.03 (95% CI: 0.003-0.099) events per PYO in the >4-year period post-treatment. When analyzed separately, both moderate and severe bleeding events showed significant reductions. The rate of severe bleeding events decreased from 0.89 events per PYO before treatment to 0.08

events per PYO in the 12 months post-treatment, while moderate bleeding events decreased from 1.11 to 0.72 events per PYO in the same period.

Notably, there was a transient increase in the rate of moderate bleeding events in the first 6 months post-treatment (1.28 events per PYO), which then decreased substantially in subsequent periods. Throughout the entire post-treatment phase, only four severe bleeding events were reported, with two occurring in the first 6 months after WASKYRA infusion. No Grade 4 severe bleeding events were reported up to the data cut-off in any of the studies. The most frequent moderate and severe bleeding events both before and after treatment were petechiae, with other common events including hemorrhagic diarrhea, epistaxis, and gastrointestinal hemorrhage.

Figure 2. Moderate and Severe Bleeding Events Over Time in WASKYRA-Treated Patients



Source: Module 2.5 Clinical Overview Addendum
Abbreviation: FU, follow-up; GT, gene therapy

Safety

The safety evaluation of WASKYRA is based on comprehensive data from 27 patients with WAS treated across two clinical studies (TIGET-WAS and OTL-103-4) and the EAP. The median age at treatment was 2.56 years with a range from 0.98 to 35.1 years.

Mortality and Serious Adverse Events

One death occurred in the study population involving a 35-year-old patient who died approximately 4.5 months after treatment due to deterioration of a preexisting neurological condition. This death is considered unrelated to WASKYRA, though

relatedness to the conditioning regimen could not be definitively excluded. A total of 67 serious adverse events (SAEs) were reported in 22 patients (81.5%), with the majority occurring within the first 6 months post-treatment during the period of immune reconstitution. The most common SAEs included device-related infections, pyrexia, and gastroenteritis. Importantly, none of the SAEs were considered related to WASKYRA treatment itself.

Common Adverse Events

All patients experienced at least one adverse event (AE) during the study period, which is expected given the underlying immunodeficiency condition and the intensive conditioning regimen required for treatment. The most frequently reported AEs included upper respiratory tract infections (85.2% of patients), anti-platelet antibody positivity (74.1%), pyrexia (74.1%), anemia (70.4%), and various manifestations including diarrhea, eczema, liver injury, and petechiae, each occurring in approximately two-thirds of patients.

Adverse Events of Special Interest

Several categories of AEs required particular attention due to their clinical significance or theoretical risks associated with GT. Two patients experienced prolonged neutropenia within the first 30 days post-treatment; both cases resolved without sequalae. One patient developed veno-occlusive liver disease (VOD) on Day 9, which resolved by Day 42 and was attributed to the busulfan conditioning regimen. Immune-mediated events occurred in nine patients (33.3%), including immune thrombocytopenia and autoimmune neutropenia, which generally resolved during the post-treatment period without requiring long-term immunosuppression.

Oncogenicity Assessment

Given the use of LVVs that integrate into the patient's genome, careful monitoring for insertional oncogenesis was conducted throughout the study period. No evidence of abnormal clonal proliferation, insertional mutagenesis, or leukemia was observed in any patient. One case of papillary thyroid cancer occurred 5 years post-treatment, but this was considered possibly related to the conditioning regimen and prior immunosuppression rather than to WASKYRA itself. The tumor tissue analysis did not reveal viral vector gene sequences supporting this assessment.

The overall safety profile of WASKYRA is considered acceptable for the treatment of severe WAS. The majority of AEs were attributable to the underlying disease pathophysiology, the intensive conditioning regimen consisting of rituximab, busulfan, and fludarabine, or the expected period of immune reconstitution following treatment. No AEs were directly attributed to WASKYRA itself, and the observed safety profile aligns with expectations for a GT requiring myeloablative conditioning in an immunocompromised patient population.

Long-Term Monitoring and Risk Management

Recognizing the limitations of the relatively small safety database and the theoretical long-term risks associated with lentiviral GT, a comprehensive post marketing requirement has been established (See Section III for details).

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for the Applicant and one foreign clinical study site that participated in the conduct of Protocols 201228 (TIGET-WAS) and OTL-103-4. The inspections did not reveal significant issues that impacted the data submitted in this original Biologics License Application (BLA).

c. Pediatrics

The WASKYRA clinical development program included patients 0.98 to 35.1 years old with a median age of 2.6 years. Only two patients treated with WASKYRA were adults. No patients younger than 6 months of age was treated in WASKYRA clinical program. Considering risks associated with treatment procedure such as leukapheresis in infants and lack of clinical experience in pediatric patients < 6 months of age, it is recommended that WASKYRA use be limited to pediatric patients 6 months and older.

d. Other Special Populations

Immune deficiency is a hallmark of WAS. All patients treated in the WASKYRA clinical development program were considered immunocompromised.

IV. Safety and Pharmacovigilance

Pharmacovigilance

The Pharmacovigilance Plan (PVP) for WASKYRA (BLA 125846/0.19), received July 18, 2025, includes the Applicant's assessment of important identified risks, important potential risks and missing information. There was no important identified risk identified by the Applicant. Important potential risks include malignancy due to insertional oncogenesis. Missing information includes long term safety.

The Applicant will conduct routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80 and enhanced pharmacovigilance for secondary (i.e. post treatment) malignancies. Enhanced pharmacovigilance will include expedited (15-day) reporting of all secondary malignancies regardless of seriousness of the event or label status. In addition, the applicant agrees to provide aggregate safety assessments for the risk of all reported malignancies, specifying the data sources for reports of malignancy for each reporting period.

In addition to routine and enhanced pharmacovigilance, the Applicant will conduct an observational postmarketing safety study as a postmarketing requirement (PMR) under 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA), to assess and characterize the risk of secondary malignancies and long-term safety following treatment with WASKYRA. This study will enroll 14 patients with WAS with a long term follow up (LTFU) for up to 15 years after infusion. This LTFU aligns with the FDA Guidance "Long Term Follow-up After Administration of Human Gene Therapy Products" (January 2020), which recommends 15 years LTFU for gene therapies with integrating vectors (such as lentiviral vectors) available at https://www.fda.gov/media/113768/download. The following milestones have been established for the PMR study:

Final Protocol Submission: January 30, 2026
Study Completion Date: June 30, 2046
Final Report Submission: December 31, 2046

The proposed pharmacovigilance plan for WASKYRA is adequate for the labeled indication. The available data does not indicate a safety signal that would require a Risk Evaluation and Mitigation Strategy (REMS). There is no agreed upon safety postmarketing commitment (PMC) for this product.

4. Labeling

The proposed proprietary name, WASKYRA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on March 31, 2025, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on April 9, 2025.

APLB reviewed the proposed prescribing information and package and container labels on July 15, 2025, and found them acceptable from a comprehension, readability, and promotional perspective.

The Office of Review Management and Regulatory Review (ORMRR) and the Office of Gene Therapy (OGT) reviewed the package and container labels and determined they meet regulatory/statutory requirements.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

Several significant labeling changes were made to enhance clarity and completeness of prescribing information. The indication was revised to specify that WASKYRA is indicated for WAS patients 6 months of age and older with mutation in WAS gene and in whom HSCT is appropriate. The Warning and Precautions section was expanded to include warning about serious infections. The adverse reactions section was revised to comprehensively capture safety events occurring during the conditioning period and throughout the first year following WASKYRA administration. Additionally, the Clinical Studies section was restructured to provide a comprehensive description of the pivotal study that established substantial evidence of WASKYRA's efficacy with clinically meaningful endpoints.

5. Advisory Committee Meeting

The submitted information, including clinical study design and trial results, did not raise unresolved scientific or regulatory questions that would benefit from advisory committee discussion. Therefore, this BLA was not referred to an Advisory Committee.

6. Other Relevant Regulatory Issues

WASKYRA received Orphan Drug, Rare Pediatric Disease, and Regenerative Medicine Advanced Therapy designations. The application was reviewed under the Priority review timeline and included a major amendment that extended the timeline with up to an additional three months of review.

V. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant provided substantial evidence of effectiveness and reasonable assurance of safety based on adequate clinical investigations. The review team recommends approval of WASKYRA 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 and for whom hematopoietic stem cell transplantation (HSCT) is appropriate and no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

b. Benefit/Risk Assessment

Treatment with WASKYRA demonstrated clinically meaningful and sustained reductions in severe infection rates and moderate to severe bleeding events compared to patients' pre-treatment baseline rates, with durability confirmed through extended follow-up periods spanning several years. The identified risks associated with WASKYRA treatment are primarily attributable to the myeloablative conditioning regimen and the theoretical potential for insertional mutagenesis inherent to lentiviral gene therapy, both of which are appropriately mitigated through routine pharmacovigilance measures and a mandatory 15-year post-marketing safety study. The overall benefit-risk profile supports a favorable assessment for WASKYRA in patients with WAS without suitable HSCT donor.

The clinical trial data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS). However, a 15-year safety PMR study is required to assess the risk of secondary malignancies and long-term safety following treatment with WASKYRA.

c. Recommendation for Postmarketing Activities

The Applicant agreed to the following PMRs:

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.

   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.

   Final Protocol Submission: March 31, 2026

   Study Completion Date: September 30, 2026

   Final Report Submission: December 31, 2026

The Applicant agreed to the following CMC PMCs:

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.

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.

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.

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.

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.

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.

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.

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.

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.

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”

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.

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.

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.

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.

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.