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Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Office of Biostatistics and Pharmacovigilance (OBPV)  
Division of Pharmacovigilance (DPV)**

**PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

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**Subject:** Review of Pharmacovigilance Plan for Telethon003

**Sponsor:** Fondazione Telethon ETS

**Product:** WASKYRA (Etuvetidigene autotemcel); Telethon003

**Application Type/Number:** BLA 125846/0

**Proposed Indication:** 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 stem cell donor is available

**Submission Date:** January 10, 2025

**Action Due Date:** December 10, 2025

## 1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the BLA 125846/0 based on the safety profile of Telethon003 (TL003) (WASKYRA; etuvetidigene autotemcel). Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for Telethon003 (etuvetidigene autotemcel). Please refer to the Appendix for the complete list of materials reviewed for this memorandum.

## 2 BACKGROUND

Wiskott-Aldrich syndrome (WAS) is a rare X-linked immunodeficiency disorder usually seen in males. The estimated incidence for WAS is 1 in every 100,000 live births.<sup>1</sup> It is characterized by a combination of various symptoms including eczema, immunodeficiency, autoimmune disorders, thrombocytopenia and increased susceptibility to develop malignancies. Various mutations in the gene encoding Wiskott-Aldrich syndrome protein (WASP) – a key regulator of signaling and cytoskeletal reorganization in hematopoietic cells – are the underlying cause of this disorder.<sup>2</sup> Mutations in WASP lead to a spectrum of clinical manifestations which is usually assessed using a 5-point scale scoring system developed by Zhu et al. Scores  $\geq 3$  are synonymous with a severe form of the disorder.<sup>3</sup> Although there is no absolute genotype-phenotype association, three main classical associations have been identified:

- 1) Classic (severe) WAS – involves the absence of WASP, causing bacterial and viral infections, severe eczema, autoimmunity and/or malignancy.
- 2) X linked thrombocytopenia (XLT) – involves mutations impairing WASP, causing less severe or absent infections, thrombocytopenia, and eczema.
- 3) X linked neutropenia (XLN) - characteristic for infections associated with neutropenia and involves gain-of-function mutations in the WASP gene.

Treatment options for WAS currently includes allogenic hematopoietic stem cell transplant (HSCT) and individualized preventive and supportive management based on clinical manifestations of the disease. The Applicant highlights that in contrast to HSCT, "Telethon003 involves the use of an autologous procedure that does not require any donor search. Furthermore, it is not associated with any risk of GvHD and can be performed after reduced intensity conditioning (RIC), as incomplete chimerism does not pose any safety risk thereby limiting the risk of conditioning-related toxicity" (pg.14, module 2.5 Clinical Overview).

The life expectancy for X-linked thrombocytopenia is close to that of the normal population; however, classic WAS has a poor prognosis. The most frequent cause of death for WAS patients is bleeding.<sup>4</sup>

### 3 PRODUCT INFORMATION

#### 3.1 Product Description

Telethon003 (TL003) is a genetically modified autologous CD34+cell population containing hematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* with a replication-incompetent lentiviral vector (LVV) encoding the human Wiskott-Aldrich Syndrome (WAS) gene.

Autologous CD34+ HSPCs are mobilized from the bone marrow to the peripheral circulation where they are harvested, (b) (4), and transduced with the lentiviral vector. Transduction allows the insertion of (b) (4) functional copies of the WASP complementary deoxyribonucleic acid (cDNA) into the cell's genome. These genetically modified cells are now capable of expressing the functional WASP.

Telethon 003 will be supplied as a cryopreserved formulation manufactured from mPB in one or more 50 mL (nominal volume) ethylene vinyl acetate (EVA) infusion bag(s) at a concentration of  $2 \times 10^6$  viable cells per mL, in a volume of 10 to 20 mL of cryopreservation medium (5% dimethyl sulfoxide (DMSO), 7% human serum albumin (HAS) and 0.9% saline solution) per EVA bag.

Telethon003 will be administered via intravenous infusion, after thawing, without any further manipulation, as a one-time treatment for autologous use only.

The minimum recommended dose is  $7 \times 10^6$  CD34+ cells/kg.

#### 3.2 Proposed Indication

As listed by the Applicant in the proposed U.S. Prescribing Information (USPI) submitted to BLA 125846/0.1:

“WASKYRA is indicated for the 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 stem cell donor is available.”

OBPV defers to the product office on the final language for the indication statement. Please see the final version of the package insert submitted by the Applicant for the final agreed-upon indication after FDA review.

### 4 PERTINENT REGULATORY HISTORY

On January 10, 2025, the Applicant submitted final documents for this BLA submission. On March 11, 2025, FDA sent the Applicant a filing notification and classified this application as Priority Review with a goal review date of September 10, 2025. Due to additional information submitted regarding an assay for the testing of WASP which resulted in a Major Amendment, this action due date was changed to December 10, 2025 (with a revised internal action due date of October 31, 2025). Telethon003 (etuvetidigene autotemcel/Waskyra) met the criteria for priority review as this product currently holds Rare Pediatric Disease Designation (RPD-2017-142) since 2018, FDA orphan drug designation since 2010 (10-3043), and regenerative medicine advanced therapy designation since 2019 (RPD-2017-142).

Telethon003 has not been approved for marketing in any other country.

## 5 DESCRIPTION OF TELETHON003 CLINICAL TRIAL SAFETY DATABASE

### 5.1 Clinical studies and Expanded Access Program

The clinical study safety data reviewed are from the Clinical Overview, Clinical Study Reports and Summary of Clinical Safety submitted to STN 125846/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the Applicant data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125846/0 be approved. Please refer to the package insert for the final clinical safety data.

The clinical development program for Telethon003 consists of two studies and one expanded access program described in table 1.

**Table 1: Summary of Clinical Studies and Programs for Telethon003 supporting the safety of Telethon003**

Trial/Study	Number of subjects	Description
Study TIGET-WAS (201228), NCT01515462, EudraCT 2009-017346-32	8	Phase I/II, open label, single arm, non-randomized, prospective, single center study. <u>Cell Source for drug product (DP) manufacturing</u> : bone marrow (BM) (n=5), mobilized peripheral blood (mPB) (n=2), BM and mPB (n=1) Fresh formulation of Telethon003 was used
Study OTL-103-4, NCT03837483, EudraCT 2018-003842-18	10	Phase III, open label, single arm, non-randomized, multi-center study Cell source for DP manufacturing: mPB (n=10) Cryopreserved formulation of Telethon003 was used
Expanded Access Program (EAP): Hospital Exemption (HE) 205030 and Compassionate Use Program (CUP) 206257	10 (3 from HE and 7 from CUP)	Prospective single center treatment program for patients with WAS. Patients were treated with Telethon003 under the provisions of HE/Compassionate Use in Italy. Cell source for DP manufacturing: mPB (n=9) Fresh formulation of Telethon003 was used

For all studies/programs listed below, the most common adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESI) are listed according to the treatment phase in which they occurred. Each study/program involved three treatment phases as described below.

1. Pre-treatment – Date of screening to the day before on treatment
2. On-treatment – Day of peripheral blood stem cell (PBSC) mobilization or from day - 22(+/-1) up to and including Day 1 (day of Telethon003 infusion)
3. Post-treatment – Day after Telethon003 infusion to data analysis cutoff date

### 5.1.1 Study TIGET-WAS

**Study Title:** A phase I/II, open label, single arm, non-randomized, prospective, single center study using 12-month pre-treatment period as the comparator.

**Study Population:** Eight participants were enrolled in this study and completed all procedures which includes bone marrow (BM) harvest, peripheral blood stem cell (PBSC) mobilization, reduced intensity conditioning (RIC) and Telethon003 infusion. The median age at the time of gene therapy (GT) was 2.2 (1.1-12.4) years with 5 participants < 5 years old. All participants were male with a Zhu score  $\geq 3$ . Seven of the participants were white and 1 was Asian.

This study included a study period of 13.56 years as a follow up phase (initial follow-up period of 3 years after infusion of Telethon003) and a long term follow up phase (participants who completed the follow-up phase were contacted annually, to collect long-term safety and selected efficacy data) was added. All participants completed the 8-year visit, 5 completed a 10-year visit and 1 completed a 13-year visit.

The data lock point for this study was December 18, 2023.

#### **Adverse Events by Treatment Phase**

There were 140 events (70 per person-year of observation (PYO)) pre-treatment, 99 events (98 per person-year) on-treatment, and 1,123 events (13 per person-year) post-treatment. By study end, 1,062 out of 1,123 post-treatment AEs resolved with 61 ongoing.

#### **Most frequently reported AEs (rate $\geq 1$ per PYO) by treatment phase:**

- **Pre-treatment (events per PYO):** Petechiae (6.50), lymphadenopathy (3), head injury (2.50), pyrexia, headache epistaxis, rhinitis and rash (2 each), eczema (1.50), device related infection, eosinophilia, antinuclear antibody positive, streptococcus test positive, bacterial disease carrier, upper and lower respiratory tract infection, lymphadenitis, gastrointestinal hemorrhage, hypertension, and vasculitis (1.00 each)
- **On-treatment (events per PYO):** Petechiae (7.92), pyrexia, epistaxis (2.97 each), rash, rhinitis, hematochezia, hypokalemia, headache, wheezing abdominal pain, cytomegalovirus test positive, hypertension, arthralgia (1.98 each).
- **Post-treatment (events per PYO):** Upper respiratory tract infection (URI) (0.94) was the most frequently reported AE when considering all post-treatment time periods combined. By post-treatment timeframe, the most frequently reported AEs were as follows: petechiae (4.52 events), pyrexia (3.51), diarrhea and eczema (1.76 each), rash (1.51), hepatic enzyme increased, cytomegalovirus infection reactivation and drug eruption (1.25 each), rhinitis, vomiting and diaper dermatitis (1.00 each) during 0-6 months post-treatment; gingival bleeding (2), epistaxis (1.51), pyrexia (1.50), URI and petechiae (1.00 each) during the 6-12 months post-treatment ; petechiae (1.38), URI (1.25), pyrexia (1.13), eczema (1.00) during the 1- 2 year post-treatment ; URI (2.00) during the 2-3 year post-treatment. There were no AEs with a rate  $\geq 1$  during the 3-8 and >8-year period post-treatment.

#### **AEs within 48 hours of Telethon003 Infusion**

Seven AEs were reported (cholestasis, decreased appetite, headache, hepatomegaly, sinus arrhythmia, petechiae, vomiting) during that time. None of these events were classified as serious, or treatment related.

### AEs of Severe Intensity

Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 (severe) or 4 (life-threatening) AEs occurred across all phases: 18 events (62.5%) pre-treatment, 20 events (75.0%) on-treatment, and 95 events (87.5%) post-treatment. Of the post-treatment severe AEs, 63 events (75%) occurred within the first 6 months after Telethon003 infusion. Device-related infection was the most common severe AE, occurring in all phases but predominantly post-treatment.

### Short term Safety and Tolerability of the Conditioning Regimen

Analysis of AEs during the first 100 days post-Telethon003 administration identified 105 events: 39 events (days 1-30), 33 events (days 31-60), and 33 events (days 61-100). Pyrexia was the most common AE with 2 events in the first 30 days, 3 events in days 31-60, and 2 events in days 61-100.

### SAEs related to Leukapheresis, Mobilization, Conditioning, Telethon003, and Other Study Procedures

No SAEs were considered related to leukapheresis, mobilization and Telethon003. Neutropenia which led to an extension in hospitalization in one participant was considered related to conditioning. Another participant with a family history of Graves' disease developed thyroid papillary carcinoma 3–5-years post treatment; this was considered possibly related to conditioning and immunosuppression. Viral vector sequences were absent from tumor DNA except for minor contaminants also found in normal thyroid tissue, confirming the SAE was unrelated to Telethon003.

Other procedure-related SAEs (aspiration pneumonia, device-related infection/sepsis, aspergillus infection, pyrexia, influenza) mostly occurred within 6 months post-treatment and were expected because of conditioning, immune reconstitution, and central venous port installation.

### Absolute Neutrophil Count (ANC)

All participants achieved hematological reconstitution (ANC  $>0.5 \times 10^9$  cells/L) by day 60. ANC increased through day 60, then remained stable within normal range from day 180 through  $>8$  years post-treatment.

### Adverse Events of Autoimmunity, Immune mediated AEs, and Immunogenicity

All participants experienced autoimmunity AEs across treatment phases: 6 events pre-treatment, 1 on-treatment, and 40 post-treatment. Anti-platelet antibody positivity was most the most frequent event reported (1 on-treatment, 14 post-treatment). Four clinical autoimmunity manifestations events of immune thrombocytopenia (1 pre-treatment, 1 within 0-6 months post-treatment), enterocolitis (1 prior to pre-treatment), and Henoch-Schönlein purpura (1 event  $>8$  years post-treatment) were reported. All autoimmunity AEs were attributed to underlying disease.

Thirty-two immune-mediated AEs occurred post-treatment, with 27 vasculitis events in one participant who had pre-existing vasculitis.

Two participants had autoinflammatory events. One with arthritis history experienced persistent foot/knee cellulitis, inflammation, and vasculitis throughout post-treatment and was diagnosed with familial Mediterranean fever in year 6. The second had pre-existing granulomatous perianal disease, pyoderma gangrenosum, and arthritis, with continued arthritis and vasculitis during on-treatment.

### Replication competent lentivirus (RCL), Abnormal Clonal Proliferation (ACP) and Integration Site Analysis

RCL was negative for all participants. There were no signs of insertional mutagenesis or ACP.

### Immunogenicity

There were no reports of antibodies to Wiskott-Aldrich Syndrome Protein (WASP).

### Integration Site Analysis

Integration sites in peripheral blood or bone marrow cells showed no single site contributing >30% of total retrieved sites, consistent with absence of abnormal clonal proliferation.

### Study Withdrawals and Death

No study withdrawals or deaths were reported in this study.

*Reviewer Comment: This study assessed only SAEs for procedural relationships (mobilization, leukapheresis, conditioning), not all AEs. The applicant acknowledges this may have underestimated procedure-related AEs by missing non-serious events, incompletely characterizing Telethon003's procedure-related safety profile. Most AEs, particularly during pre- and post-treatment phases, were associated with underlying WAS. Post-treatment had the highest event frequency, with majority occurring 0-6 months post-treatment—expected following conditioning regimen and immune reconstitution. Most identified SAEs were anticipated based on Telethon003 administration procedures.*

*One carcinogenic event, thyroid papillary carcinoma, occurred 5 years post-treatment in a participant with a family history of nonmalignant thyroid disease. This event resolved with sequelae (iatrogenic hypothyroidism) following total thyroidectomy. Prior to being diagnosed with thyroid carcinoma, this participant experienced high levels of thyroid stimulating hormone receptor antibodies. In the safety population, blood thyroid stimulating hormone was identified as one of the most frequently reported adverse events, occurring in  $\geq 10\%$  of the population; 5 patients who received Telethon003, were identified with elevated blood TSH levels. The proposed label for telethon003 includes a section under Warnings and Precautions which recommends monitoring of thyroid function and structure as a precautionary measure given this SAE and thyroid abnormalities in patients.*

*While lentiviral vector-infected cells can become cancerous through oncogene activation or tumor suppressor gene inactivation<sup>5</sup>, vector copy number analysis found no viral gene sequences in thyroid tumor cells except contaminants also present in normal tissue. The investigator concluded this SAE was unrelated to Telethon003, which this reviewer agrees with based on analysis results. The SAE was considered possibly related to conditioning and immunosuppression from use of busulfan (a known carcinogen).<sup>6</sup>*

### **5.1.2 Study OTL-103-4**

**Study Title:** A phase III, open label, single arm, non-randomized multi-center study using the 12-month pre-treatment period as a comparator.

**Study Population:** Ten male participants completed all procedures including bone marrow harvest, peripheral blood stem cell mobilization, reduced intensity conditioning, and Telethon003 infusion. Median age at gene therapy was 1.9 years (range 1-9), with five participants under 5 years old. All had Zhu scores  $\geq 3$  except one with score 2 whose disease

was considered severe due to genetic mutation causing large protein truncation. Six participants were White, 2 were Asian, and 2 were Black/African American.

Study duration was 4.87 years with interim analysis data cutoff December 4, 2023. All participants received Telethon003 with follow-up ongoing.

#### Adverse Events by Treatment Phase

A total of 413 AEs were reported: 80 events (58.79 per person-year) pre-treatment, 84 events (51 per person-year) on-treatment, and 310 events (9.60 per person-year) post-treatment. Most post-treatment AEs occurred within 6 months (140 events; 28.10 per person-year). At data cutoff, 61 AEs (14.7%) remained unresolved; none were SAEs, though two severe AEs (erosive gastritis and esophageal candidiasis) were ongoing but clinically resolved pending confirmatory endoscopy.

#### **Most frequently reported AEs (rate $\geq 1$ per PYO) by treatment phase:**

- **Pre-treatment events per PYO):** Petechiae and CMV infection (3.67), anemia and antiplatelet antibody positivity (2.94 each), head injury, epistaxis, rhinitis, iron deficiency, constipation and staphylococcus test positive (1.47 each) were also frequently reported.
- **On-treatment (events per PYO):** Petechiae (3.05) most common; drug hypersensitivity and cellulitis (2.44 each), anemia, head injury, device related infection, urticaria, catheter site hemorrhage (1.83 each), vomiting, rash, hepatic enzyme increased, abdominal pain, aspartate aminotransferase increased, bronchospasm, clostridium difficile infection, laryngospasm (1.22) was also reported.
- **Post-treatment (events per PYO):** Upper respiratory tract infection (0.62) was the most frequently reported AE overall across all post-treatment periods. By post-treatment time frame, the most frequently reported AEs were: petechiae, vomiting, rash (1.20 each), and eosinophilia (1.00) were frequently reported during the 0-6 months post-treatment period; URI (1.17 and 1.00) during the 1-2 year and 2-3-year post-treatment periods respectively. During the 6-12 month and 3-5-year post-treatment periods, no AEs occurred rates  $\geq 1$  event per PYO.

#### AEs within 48 hours of telethon infusion

Two AEs occurred within 48 hours post-Telethon infusion: otorrhea and hepatic enzyme increase. The participant with hepatic enzyme increase was subsequently diagnosed with veno-occlusive disease, classified as a severe SAE related to conditioning.

#### AEs of Severe Intensity

Severe intensity AEs (CTCAE Grade 3+) occurred across all phases: 18 pre-treatment, 27 on-treatment, and 44 post-treatment, with 38 of the 44 post-treatment events in the first 6 months. Most common severe AEs were device-related infection, anemia, febrile neutropenia, immune thrombocytopenia, and neutropenia.

Two Grade 4 events were classified as SAEs: autoimmune neutropenia (first 6 months post-infusion) and thrombosis with thrombocytopenia syndrome/post-vaccination thrombocytopenia (3-5 years post-infusion).



### Short term Safety and Tolerability of the Conditioning Regimen

The most common AEs within 100 days of Telethon003 infusion were rash, vomiting, and febrile neutropenia. Two conditioning-related SAEs of thrombotic angiopathy (day 9) and veno-occlusive liver disease (day 18) occurred due to higher doses of Busulfan administered.

### AEs related to Leukapheresis, Mobilization, Conditioning, Telethon003, and Other Study Procedures

Stomatitis, vomiting, aphthous ulcers, mucosal inflammation, urticaria, hepatic enzyme increase, and transfusion reaction were considered possibly related or related to conditioning. Catheter and device-related infections were considered related to other study procedures. Gastrointestinal symptoms following plerixafor administration were considered related to CD34+ cell mobilization.

Due to a programming error, bronchospasm and transaminase elevation were omitted from analysis but were considered probably related to leukapheresis and conditioning, respectively, per the study report.

Per the Applicant, there were no AEs considered related to Telethon003.

### SAEs related to Leukapheresis, Mobilization, Conditioning, Telethon003, and Other Study Procedures

The conditioning-related SAEs veno-occlusive liver disease and thrombotic angiopathy occurred in one participant who received significantly elevated busulfan doses. Of two participants with high busulfan exposure, only one developed SAEs, prompting a protocol amendment for flexible busulfan dosing. Other procedure-related SAEs included device-related infection, device-related sepsis, pseudomonal sepsis, and catheter site hemorrhage.

No SAEs were attributed to leukapheresis, mobilization, or Telethon003. All SAEs had resolved by data cutoff.

### Absolute Neutrophil Count (ANC)

Ninety percent of participants achieved an ANC >500 cells/ $\mu$ L by day 60. One participant with and SAE of autoimmune neutropenia reached this threshold by day 90. However, bone marrow aspirates on days 27 and 41 showed recovery evidence which resulted in this event not being considered engraftment failure. Autologous HSPC backup was not administered.

### Adverse Events of Autoimmunity, Immune-mediated and Dermatological AEs

Thirty-two investigator-defined autoimmunity AEs occurred: 23 (71.9%) were blood autoantibodies, while others were clinical autoimmunity manifestations. Iridocyclitis and psoriasis occurred during pre- and on-treatment phases; psoriasis was later reclassified as mixed autoinflammation/autoimmunity.

Post-treatment autoimmune events included neutropenia and immune thrombocytopenia (0-6 months), uveitis (1-3 years), and thrombosis with thrombocytopenia syndrome plus thrombocytopenia (3-5 years). The latter two were cautiously classified as potentially autoimmune since autoimmune components could not be ruled out.

Autoinflammatory events included psoriasis and vasculitis (pre-treatment), autoinflammatory disease (on-treatment), and autoinflammatory joint pain (0-6 months post-treatment).

Most common dermatological AEs were skin rash and eczema, predominantly during on-treatment and 0-6 months post-infusion

#### Replication competent lentivirus (RCL), Abnormal Clonal Proliferation (ACP)

All participants tested negative for HIV-1 p24 and HIV-1 p24 binding antibody. No abnormal clonal proliferation was reported. One participant had a positive HIV-1 viral load test, which the applicant states was conducted in error.

#### Integration Site Analysis

Integration site analysis of peripheral blood and bone marrow cells showed no single site contributing >30% of total retrieved sites, consistent with absence of abnormal clonal proliferation.

#### Immunogenicity

No antibodies to WASP were reported.

#### Withdrawals and Deaths

There were no withdrawals or deaths in this study.

*Reviewer Comment: In this study, the AEs and SAEs were assessed for relatedness to leukapheresis, mobilization, conditioning and Telethon003. During the on-treatment and 0–6-month post-treatment period, when immune reconstitution was most pronounced, the majority of adverse events occurred and were attributed to either catheter-related complications or manifestations of the underlying disease. Two AEs considered possibly related to leukapheresis and conditioning, each occurring in one participant (bronchospasm and transaminase elevation, respectively), were omitted from the analysis due to an error in programming. Two conditioning-related SAEs (thrombotic microangiopathy and veno-occlusive disease) resulted from high busulfan doses. The applicant adequately addressed this safety issue through protocol amendments to ensure patient safety.*

*For the positive HIV-1 viral load test, the applicant states that this test was done in error and was not part of the protocol “due to the possibility of false positive results arising from the HIV-1 derived lentiviral vector used for gene transduction.” Further review of the protocol for monitoring of RCL (page 79 and 80 of the OTL Study Body Report) confirmed the exclusion of this test. Testing involves “an (b) (4) for HIV-1 p24 antigen in serum. Should a test be positive for HIV-1 p24, confirmation via 2<sup>nd</sup> level testing.” To address this issue post marketing, the Warnings and Precautions section of the draft label (Section 5.10) includes “interference with HIV testing.”*

*At the time of data cut off, this study was ongoing with 61 AEs unresolved; however, no unresolved AEs were classified as SAEs per the applicant.*

### **5.1.3 Expanded Access Program**

Study Title: A prospective single center treatment program for WAS patients with unmet medical needs in anticipation of the product's commercial availability

Study Population: Ten participants were enrolled across both programs: 3 in the Hospital Exemption (HE) program and 7 in the Compassionate Use Program (CUP). Nine participants completed all procedures which includes BM harvest, PBSC mobilization, RIC and Telethon003 infusion. One participant in the CUP did not receive RIC or Telethon003 due to the low yield of CD34+ cells during harvesting. Another participant passed away approximately 4 months post

telethon infusion. Eight participants remained in the program through completion. By the data cut-off, October 24, 2023, 8 participants had completed the Year 3 visit, 7 participants had completed the Year 5 visit, and two participants had completed the Year 7 visit. The median duration of follow up in the surviving participants in the Intention to Treat (ITT) population was 5.9 (4.73-7.44) years. The median age at the time of GT was 3.8 (1.4 to 35.1) years. Five participants were < 5 years old of which 2 were < 2 years old. Three participants were > 11 years olds of which two were adults. All participants were male and had a Zhu score  $\geq 3$ . Among the participants who received Telethon003, 7 were white, 1 was Asian and 1 was American Indian/Alaska Native.

The study period for this program was 7.87 years with data cut off dates of October 17 and 10, 2023, for the HE and CUP, respectively.

### Adverse Events

The pre-treatment phase included 128 AEs reported in all mobilized participants (n=10), which decreased to 102 events during on-treatment. Post-treatment phase recorded 421 events in 9 participants, with the majority (172 events) occurring during the 0–6-month period. By the final analysis cutoff date, 369 of 421 post-treatment AEs had resolved with 51 reported as ongoing.

### **Most frequently reported AEs (rate $\geq 1$ per PYO) by treatment phase:**

- **Pre-treatment (events per PYO):** The most frequent AE were petechiae (3.89), epistaxis and anti-platelet antibody (both 3.34), lymphadenopathy, hematochezia and antineutrophilic cytoplasmic antibody positive (2.20 each), eczema and food allergy (1.67 each), cytomegalovirus viremia, candida test positive, oral candidiasis, malocclusion, pulmonary mass, allergic conjunctivitis, haemophilus test positive antinuclear antibody positive and drug hypersensitivity (1.11 each).
- **On-treatment (events per PYO):** Petechiae (10.22), anemia (5.45), and eczema (4.77) epistaxis and vomiting (2.73 each), mouth hemorrhage, gingival bleeding hematological infection and urticaria (2.04 each), cough, diarrhea, gastroenteritis, CMV viremia, drug hypersensitivity, pain in extremity, pyrexia, dermatitis, staphylococcus test positive and blood potassium decrease (1.36 each).
- **Post-treatment:** Upper respiratory tract infections (0.55) was the most frequently reported AE overall across all post-treatment periods. By post-treatment timeframe, the most frequently reported AEs were eczema (3.44), petechiae (2.53), anemia (1.84), epistaxis, device related infection (1.38 each), pyrexia (1.15) during the 0-6 months post treatment period; petechiae (1.00) during the 6–12-months post-treatment period; and URI (1.25) during the 1–2-year post-treatment period. No AEs  $\geq 1$  event were reported during the 2-3- and 3-8-years post-treatment periods.

### AEs within 48 hours of Telethon003 Infusion

Dermatitis, mouth hemorrhage, nausea, anemia, petechiae, and increased transaminases were identified during this period. None were classified as SAEs or considered related to Telethon003.

### AEs of Severe Intensity

Severe intensity AEs predominantly occurred during on-treatment and post-treatment phases. Device-related infection was the most frequently reported severe AE across both periods. Eczema was commonly observed during on-treatment, while febrile neutropenia was frequently

reported post-treatment. Several severe AEs were classified as SAEs, including Grade 4 food allergy (pre-treatment), Grade 4 upper gastrointestinal bleed (pre-treatment), shock (on-treatment), and Grade 4 neutrophil count decrease with suspected subclinical infection (0-6 months post-treatment).

#### Short Term Safety and Tolerability of the Conditioning Regimen

Device-related infection was the most common AE during the first 30 days and 31-60 days post-treatment, with one additional case reported between 61-100 days.

#### SAEs related to Leukapheresis, Mobilization, Conditioning, Telethon003, and Other Study Procedures

Twelve SAEs were reported: acute cholangitis, congenital coronary artery malformation, device-related infection (2 events), epistaxis, EBV, gastroenteritis, measles, lymphadenopathy, neurological decompensation, UTI, and wrist fracture. Seven of these SAEs occurred within the first 6 months post-treatment, including a fatal neurological decompensation event.

Device-related infection and UTI were considered related to program procedures. Device-related infection occurred once during on-treatment and twice within 6 months post-treatment; UTI also occurred within 6 months post-treatment. Circulatory shock was considered related to conditioning, occurring during rituximab infusion.

Per the applicant, lymphadenopathy was programmatically listed as an SAE due to hospitalization but not reported as an SAE in the eCRF since hospitalization was for elective surgery.

No SAEs were considered related to mobilization, leukapheresis, or Telethon003.

#### Absolute Neutrophil Count (ANC)

No neutrophil engraftment failures occurred. All participants experienced neutropenia post-conditioning lasting 6-29 days; however, all achieved ANC  $>0.5 \times 10^9$  cells/L within 100 days of treatment. This level was sustained at all subsequent time points following the first 100 days post-Telethon003 infusion.

#### Adverse Events of Autoimmunity and Immune-mediated and Dermatological AEs

Most investigator-defined (events considered immune-related by the treating physician) and dictionary-defined autoimmunity AEs (identified using the Standardized MedDRA Query (SMQ) "immune-mediated/autoimmune disorders" in MedDRA version 26.0) were due to positive autoantibodies. Anti-platelet antibody positivity occurred during pre-treatment and post-treatment. Other positive autoimmunity events included antineutrophil cytoplasmic antibody and smooth muscle antibody positivity, both occurring pre-treatment and post-treatment.

Autoantibodies were not associated with clinical autoimmunity features in most cases. Three events involved clinical autoimmunity manifestations. Two immune thrombocytopenia cases occurred: one within 6 months of treatment resolving 29 days post-IVIG, and one Grade 4 case from  $>2$  years pre-gene therapy resolving within 6 months post-treatment. One participant with ulcerative colitis diagnosed 2 years pre-gene therapy experienced Grade 2 reactivation during 3–8-year follow-up that resolved, then another reactivation ~4 years later that remained ongoing at data cutoff.

For immune-mediated AEs using SMQ immune-mediated and autoimmunity criteria, polyarthritis and vasculitis were identified. Vasculitis occurred during the pre-treatment period; polyarthritis occurred during on-treatment.

Eczema was the most common dermatological AE across all phases with highest incidence post-treatment. Rash was also commonly reported during on-treatment and post-treatment. No autoimmunity, immune-mediated, or dermatological AEs were considered related to Telethon003 or administration procedures. No WASP antibodies were identified.

#### Replication competent lentivirus (RCL), Abnormal Clonal Proliferation (ACP)

All participants tested negative for HIV-1 p24 or HIV-1 p24 binding antibody. No evidence of abnormal clonal proliferation was reported.

#### Integration Site Analysis

Integration site analysis of peripheral blood and bone marrow cells showed no single site contributing >30% of total retrieved sites, consistent with absence of abnormal clonal proliferation.

#### Immunogenicity

No antibodies to WASP were reported.

#### Withdrawals and Deaths

One participant was withdrawn from the CUP due to insufficient CD34+ cell harvest.

One death was reported in the CUP program. A 35-year-old white male with a medical history of spastic gait died approximately 4.5 months after receiving Telethon003. His cause of death was considered related to the progression of a pre-existing neurological condition which was reported as a grade 3 AE of neurodegenerative disorder (neurodegeneration with brain iron accumulation) on day -185 during pre-treatment. Page 193 of the Clinical Program Report states that the participant's cause of death was "considered to be due to an underlying disease, which the treating physician and associated clinical center staff judged may have been a form of iron accumulation encephalopathy; however, relatedness to the conditioning regimen could not be excluded by the treating physician."

*Reviewer comment: Similar to the other studies, most of the common AEs reported were symptoms of the background disease especially during the pre and on-treatment phases. AEs were not assessed for relatedness to Telethon003, or the study procedures involved in the products administration potentially leading to underreporting of AEs which the Applicant acknowledged. This reviewer agrees with the SAEs considered related to conditioning based on the busulfan SMPC and other study procedures such as the installation of the port-a-catheter.*

*One SAE, neurological decompensation resulted in the death of one participant which was not considered related to the drug; however, the applicant did not exclude conditioning relatedness. According to the patient narrative for (b) (6), this participant was screened for the Expanded Access Program (EAP) on (b) (6), with the event neurodegenerative disorder identified on (b) (6). Telethon003 was administered on (b) (6), with study procedures for the product administration beginning (b) (6). From October 2016, 88 days post treatment the narrative states that "the patient developed neurological deterioration as he experienced "worsening of speech, more pronounced asthenia, and severe axial instability, leading to difficulties in walking for some steps and required additional support. "A brain magnetic resonance imaging (MRI) "indicated cerebellar and cortical atrophy, and bilateral T2-*

*hypointensity at the red nucleus and substantia nigra.” His condition progressively worsened which led to him being placed under palliative care.*

*The treating physician and associated clinical center staff judged that this may have been a form of iron accumulation encephalopathy, and that the participant's death was considered to be “due to an underlying disease” stating in the narrative that “there was no reasonable possibility that the neurological deterioration may have been caused by Telethon003. Other possible causes of the neurological deterioration included the patient’s medical condition and concurrent medications. The treating physician reported that they could not exclude the role of the conditioning treatment (i.e., busulfan, fludarabine).” Based on the MRI images, an expert physician consultation assessment on (b) (6) , stated that “the patient strongly deposed for a form of iron accumulation encephalopathy (i.e., a type of beta-propeller protein-associated neurodegeneration or mitochondrial membrane protein-associated neurodegeneration)”.*

*The applicant responded appropriately to this event by amending the CUP protocol which included the addition of an imaging procedure at baseline (brain MRI) for patients who, in the treating physician’s judgment, may have shown signs of central nervous system alterations. In the OTL-103-4 protocol, a brain MRI was also included as one of the baseline evaluations before gene therapy (GT) in all patients in order to evaluate any potential signs of previous hemorrhages and/or signs of any possible alterations at central nervous system level.*

#### **Drug Product Formulation**

During the first 6 months after gene therapy, pyrexia, epistaxis, petechiae, and eczema occurred at higher frequency in participants treated with the fresh formulation of Telethon003 (n=17) as opposed to participants treated with the cryopreserved formulation (n=10). Despite this, the applicant states there were “no notable difference in the safety profile between the fresh and cryopreserved formulations.”

**Reviewers comment:** *More participants received the fresh formulation of the product compared to the cryopreserved formulation (n=10) which may be the reason that more AEs were identified in this group. In addition to this, most of the AEs were typical of the background disease. Overall, the number of participants who received each formulation is too small to make any firm conclusions about differences in safety profile.*

#### **Drug Product Cell Source**

Twenty-one patients received drug product (DP) derived from mobilized peripheral blood (mPB), while five patients received DP derived from bone marrow (BM), with one patient receiving products from both cell sources.

The most frequently reported system organ class (SOC) for AEs and SAEs was infections and infestations. A higher number of AEs were reported in the BM-derived DP group (> 30% of participants) compared with the mPB-derived DP group; however, the BM-derived group had less patients.

No differences in safety profile were observed between DP derived from BM and mPB sources.

**Reviewers Comment:** *Although the sample size for the groups varied significantly, infections such as URIs, rhinitis and gastroenteritis were consistently among the most common AEs across all cell sources. This reviewer agrees with the Applicant’s assessment of the safety profile. Overall, the number of participants who received DP derived from mPB versus BM was too small to make any firm conclusions about differences in safety profile.*

### **Clinical Chemistry and Laboratory (Lab) Evaluations**

Across all studies and programs, CTCAE Grade  $\geq 3$  AEs were reported for laboratory and clinical chemistry abnormalities. Frequently reported laboratory abnormalities in 2 or more participants include febrile neutropenia, anemia, immune thrombocytopenia, neutropenia, eosinophilia, hepatic enzyme increase, hypokalemia, and hypoalbuminemia. D-dimer, aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), C- reactive protein, lactate dehydrogenase and glucose were noted to have transient shifts at baseline to high level post treatment in 50% or more participants.

The most frequently reported clinically significant chemistry abnormalities were hepatic enzyme increase, hypoalbuminemia, and hypokalemia.

**Reviewer Comments:** *Most of the laboratory and chemistry abnormalities occurred within 100 days post-treatment, which is considered a critical period for immune reconstitution. According to the applicant's clinical safety summary, the assessment during this time period relates to short-term safety and tolerability of the conditioning regimen. Overall, improvements in these abnormalities were observed in most participants after 100 days.*

### **Race and Age Assessments**

There were no notable differences in AE and SAE profiles for Telethon003 observed when assessed by age group and race. Details of age group and race categories are provided in the Summary of Clinical Safety.

**Reviewer Comment:** *There were more participants in the <5-year age group (n=18) compared to the >5-year age group (n=10). No notable safety differences were observed between age groups. A higher number of AEs were reported for the <5-year-old group however during the 3–8-year post-treatment period (442 vs 120); however, this may be due to the sample size differences.<sup>7</sup>*

## **6 SUMMARY OF POSTMARKETING EXPERIENCE**

Not applicable. Telethon003 has not yet received regulatory approval in any country.

## **7 SPONSOR'S PHARMACOVIGILANCE PLAN**

A summary of the Applicant's Pharmacovigilance Plan (PVP) is provided in Table 2 below. In addition to the routine pharmacovigilance activities, the Applicant also plans to conduct long term follow up studies (LTFU) to further evaluate safety concerns in the PVP including the important potential risk of malignancy due to insertional oncogenesis.

**Table 2.** Pharmacovigilance Plan for Telethon003

Type of Concern	Safety Concern	Proposed Action
Important Potential Risk	Malignancy due to insertional oncogenesis	<ul style="list-style-type: none"> <li>– Routine pharmacovigilance</li> <li>– Additional pharmacovigilance activities:               <ol style="list-style-type: none"> <li>1) Ongoing and follow up clinical studies/Programs (EAP: HE, CUP)</li> <li>2) Post Authorization Safety Study (PASS); Long Term Follow up efficacy and safety study (WAS-TLT003-01)</li> <li>3) Early Access Scheme in Italy under national law 648/96</li> </ol> </li> <li>- Risk minimization and communication measures as stated in Table 9, and section 6.2 of the applicant's PVP include educational materials for healthcare professionals and patients/parents/carers to facilitate informed decision-making by healthcare professionals and patients/parents based on Telethon003's benefits and risks while ensuring proper administration, monitoring, and risk minimization through comprehensive guidance on handling procedures, safety concerns, and long-term follow-up requirements.</li> </ul>
Missing Information	Information on long term safety	<ul style="list-style-type: none"> <li>- Routine pharmacovigilance</li> <li>– Additional Pharmacovigilance activities:               <ol style="list-style-type: none"> <li>1) Ongoing and follow up clinical studies/Programs (EAP: HE, CUP)</li> <li>2) Long Term Follow up efficacy and safety study (WAS-TLT003-01)</li> <li>3) Early Access Scheme in Italy under national law 648/96</li> </ol> </li> <li>- The applicant's risk minimization and communication measures, as outlined in Table 9 and section 6.2 of the PVP, include educational materials for healthcare professionals, information packs for patients and parents/carers, and controlled distribution to ensure safe administration and informed decision-making for Telethon003 treatment. These measures ensure that therapy is delivered only by adequately trained healthcare professionals while maintaining traceability of patients' cells and manufactured product between qualified treatment centers (QTCs) and manufacturing sites, facilitating informed decisions by HCPs and patient/parents/carers based on Telethon003's known benefits and risks, and</li> </ul>



		<p>minimizing patient risks through guidance on managing side effects and reporting adverse reactions.</p> <ul style="list-style-type: none"> <li>- Information on the duration of patient follow up in the clinical studies in PI along with guidance that patients are expected to/ will be asked to enroll in the LTFU for 15 years.</li> <li>- Routine risk minimization measures beyond PI include legal status restrictions, with the medicinal product subject to restricted medical prescription.</li> </ul>
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*\*Adapted from Tables 9 and 10, pharmacovigilance plan, STN 125846/0.1, Module 1.16. Risk Management (Non-REMS) and updated after review of the Pharmacovigilance Plan submitted on July 18, 2025, to STN 125846/0.21 Module 1.16.1 Risk Management (Non-REMS)*

*Reviewer Comments: WAS is extremely rare in females. Telethon003 safety during pregnancy and lactation has not been established and is not considered a relevant risk by the Applicant. According to the Applicant's Pharmacovigilance Plan, page 26 "LVV remains stably integrated within cells of human origin with a lack of evidence for germline transmission. With limited distribution of Telethon003 to hematopoietic tissues, reproductive or toxicity studies were not performed. Should pregnancy and subsequently lactation occur post-treatment either naturally or through in vitro fertilization, pregnancy after ovo preservation or any other method, the progress and outcome of such pregnancies, will be monitored with consideration as to whether additional actions are warranted and feasible to further characterize or minimize this risk." Since WAS is primarily seen in males, the applicant's plans are appropriate for Telethon003.*

*In the safety population, participants' ages at treatment ranged from 1-35 years. The Applicant does not consider data for 6 months-1-year olds "missing information" as the "benefit/risk and safety profile observed in the study population could be extrapolated to all patients aged 6 months or older." The applicant states on page 27 of the PVP, that "the rationale for the expanded population is that the pathophysiology and clinical manifestations of WAS are considered similar in patients aged < 1 year and > 12 years old as the subjects who participated in the clinical trial program. Additionally, Waskyra has the same mechanism of action for all patients ages." The Applicant's decision not to classify this as missing information is justifiable given the presented scientific rationale.*

*An IR was sent to the Applicant July 11, 2025, requesting 1) submission of expedited (15-day) reports to FAERS for all malignancies, regardless of seriousness of the event or label status, 2) provision of aggregate safety assessments (based on interval and cumulative postmarketing safety data) for the risk of all malignancies specifying the data sources for reports of malignancy, i.e., data from postmarketing safety study(ies), or data from postmarketing spontaneous reports, and 3) an update to the Pharmacovigilance Plan (submitted to BLA 125846/0.1 on January 10, 2025) to include the aforementioned enhanced pharmacovigilance activities for the Important Potential Risk of "malignancy due to insertional oncogenesis."*

*A response was received on July 18, 2025 (STN 125846/0.22), confirming the Applicant's compliance with enhanced pharmacovigilance requirements. The Applicant agreed to submit expedited 15-day reports to FAERS for all malignancies regardless of seriousness and to provide aggregate safety assessments in periodic reports with specified data sources and interim LTFU study summaries. The updated PVP was submitted with their response which included an appendix containing malignancy management instructions.*

## 6.1 Safety-related Post-marketing Studies

In addition to the PVP and routine pharmacovigilance detailed above, the applicant proposes to continue monitoring the safety of patients in the EAP which includes the CUP and HE, and a long term follow up study (WASTLT001). The title and purpose of all studies discussed earlier are provided below with a more detailed review of the LTFU study (WASTLT001).

### **EAP:**

**Hospital Exemption 205030 (HE):** In the absence of a suitable clinical trial open for enrollment, the objective of the HE program was to provide an alternative treatment option to patients affected by WAS with high unmet medical need. We anticipate postmarket safety data from these participants will be submitted via periodic reporting.

**Compassionate Use Program 206257 (CUP):** The primary objective of this compassionate use treatment program was to provide treatment for patients affected by WAS with high unmet medical need in advance of commercial availability. We anticipate postmarket safety data from these participants will be submitted via periodic reporting

**Early Access Scheme in Italy under national Law 648/96:** In addition to clinical trials, a reimbursed Early Access Scheme is currently active in Italy under national Law 648/1996 whereby EU patients may receive Telethon003. Patients receive the cryopreserved drug product that will be commercialized. Data from these participants was not formally integrated into the clinical trial database. As of June 19, 2025 (STN 125846/0.19 received June 25, 2025), 2024, 6 patients have been treated with the cryopreserved drug product as part of the Italian law n.648/1996. Participants will be enrolled and followed in the LTFU.

A more detailed review of the 15-year long term follow up study (WASTLT001) proposed by the sponsor according to the FDA guidance document "Long Term Follow-up After Administration of Human Gene Therapy Products" is provided below.

Study Title: A Long-term Follow-up Study for subjects previously treated with Autologous ex vivo Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy for Wiskott-Aldrich Syndrome (WAS)

Study Design: A low risk, phase III clinical study that involves the collection of long-term safety and efficacy data for patients treated with Telethon003 retrospectively and prospectively.

Study Objectives: To characterize the long-term safety and clinical efficacy of Telethon003 treatment

Study Population: The study targets 40 WAS patients treated with Telethon003 across clinical and post-marketing settings, including 26 patients from clinical development, 3 from the Early Access Scheme and 14 patients from the post-marketing settings. Sample size determination was based on Telethon003's - safety profile, existing follow-up data, and practical recruitment considerations rather than statistical power calculations.

### Variables, data collection and biospecimen data

The study will collect comprehensive patient, disease, and treatment-related variables as specified in protocol WAS-TLT003-01, with retrospective patients having clinical and gene therapy data gathered from their clinical trial/EAP conclusion through study initiation, while all

participants will undergo assessments per protocol detailed in Tables 2 and 3 during the 1-5 year and 5–15-year post- Telethon003 periods.

### **Safety Analysis**

AEs and SAEs will be summarized from LTFU study entry with annual assignment based on onset dates, presented as rates per person-year of observation, and tabulated by severity and gene therapy relationship. The primary efficacy endpoint of overall survival and secondary endpoint of long-term clinical efficacy will be analyzed per LTFU protocol specifications, with biennial interim analyses of primary endpoints and a final analysis upon the last participant's completion.

The Applicant's proposed the following milestones:

- Final protocol submission: November 30, 2025
- Study completion date: December 31, 2044
- Final study report submission: June 30, 2046

Given the potential for malignancy from insertional oncogenesis and the necessity for long-term safety surveillance, a post-marketing requirement (PMR) study is recommended.

*Reviewer Comments: On June 4, 2025, DPV met with the clinical team to discuss the LTFU submitted with the Applicant's application and the need for a PMR for WASKYRA. Due to the use of an integrating lentiviral vector and per the guidance document "Long Term Follow-up After Administration of Human Gene Therapy Products" it was concluded that this product requires a PMR should it be approved. However, the team had recommendations and needed protocol clarifications. On June 18, 2025, DPV sent an information request (IR) to the Applicant regarding the WASKYRA long-term follow-up protocol seeking clarification on study design classification (interventional versus observational), with FDA suggesting separation into distinct studies for clinical trial patients and post-marketing commercial patients. The second question addressed patient enrollment plans, requesting specific numbers of post-marketing patients to be enrolled and clarification about including a participant from the TIGET study who was nearing the end of a 15-year observation period. The third question focused on sample size determination for post-marketing patients, requesting justification for proposed numbers, confirmation of 15-year follow-up periods, a protocol synopsis emphasizing secondary malignancy assessment, details on sample collection and testing procedures, and specific milestone dates for protocol submission, study completion, and final reporting.*

*On June 25, 2025 (STN 125846/0020), the Applicant responded stating that "the Applicant defined the study as interventional because the evaluations required by the study protocol are not foreseen as per clinical practice." They justified combining clinical trial and post-marketing patients into a single study because "both groups follow the same safety and efficacy schedule of assessments" and "running a separate study for commercial patients only, would double the efforts and costs associated with conducting these studies." Regarding enrollment, they clarified that "there are 26 patients from clinical development expected to be included in the LTFU study, which foresees to enroll 40 patients in total" with "14 patients left to be enrolled from the post marketing setting." The Applicant further clarified that "6 patients treated under the Italian law n. 648/1996 (as of 19 June 2025) and an additional 2-3 potential patients treated under Italian law n. 648/1996 in 2025" will be enrolled in the postmarketing study. As a result, "there will be a minimum of 5 to 8 future patients who will be treated in the pure post marketing setting requiring 2-3 years to recruit these patients." For participants with 15-year follow-up, the Applicant confirmed "data for these patients up to 15 years of follow up will be captured in the LTFU*

study" and "after 15 years of long term follow up, patients are considered to have completed the LTFU study."

The applicant outlined comprehensive safety objectives, stating that "the primary objectives of the LTFU study is to characterize the long-term safety of the Telethon003 gene therapy treatment" including "insertional mutagenesis and oncogenesis (blood and solid malignancies); transgene immunogenicity; development of replication-competent lentiviruses (RCL); integration site analysis (ISA) [and] abnormal clonal proliferation (ACP)." They detailed their monitoring approach, explaining that "blood samples for ISA would be collected annually until 15 years of follow up" and "samples collected during the follow-up visits will be stored at the clinical sites and analyzed only in case of clinical need, such as suspicion of abnormal clonal proliferation." The study milestones above under the section Safety Analysis were provided by the Applicant.

On July 10, 2025, the aforementioned postmarketing safety study was presented to the Safety Working Group (SWG) with recommendations to consider this study as a Title IX Postmarketing Requirement (PMR). The rationale included 1) to be consistent with the FDA guidance which recommends 15 year long term follow up (LTFU) for gene therapies with integrating vectors (such as lentiviral vectors), 2) to identify an unexpected serious risk (secondary malignancies) when available data indicates the potential for a serious risk and 3) to ensure consistency in regulatory requirements across product in a similar class (all integrating vector gene therapies have 15-year LTFU PMR studies to assess the risk of secondary malignancy). In addition, the CBER Surveillance Program (CSP) team performed an Active Postmarket Risk Identification and Analysis (ARIA) assessment and determined that the pharmacovigilance system FDA is required to maintain under section 505(k)(3) of the FDCA (the Sentinel program) is not sufficient to evaluate this serious risk. The evaluation of the serious risk of secondary malignancies associated with WASKYRA requires a long follow up period (15 years) and collection of tumor tissue and analysis for persistence of the vector used in WASKYRA is not feasible in claims-based data sources like the CBER Sentinel program. The details of this assessment were documented in a memorandum finalized June 9, 2025. SWG concurred with the recommendation to classify this postmarketing safety study as a PMR.

On July 11, 2025, FDA sent an IR to the Applicant requesting a detailed proposal for a prospective, observational study to assess long-term safety and secondary malignancy risks over 15 years post-treatment, including target enrollment based on disease incidence and projected commercial use, plus specific milestone dates for protocol submission, study completion, and final report submission. Second, FDA required acknowledgment that the final protocol would describe sample collection methods ensuring healthcare providers report neoplasms within 72 hours for tumor specimen processing, and include detailed testing algorithms (vector copy number, integration site analysis) to evaluate WASKYRA's potential causal role in malignancies. Third, FDA acknowledged the proposed post-approval safety study protocol WAS-TLT003-01 and indicated the post-marketing observational study could be incorporated as a cohort under this protocol if separate milestone dates, analysis, and target enrollment were planned.

A response to this IR was received from the Applicant on July 16, 2025 (STN 125846/0.22). First, regarding the post-marketing study proposal, the applicant confirmed their Long Term Follow Up (LTFU) study addresses the 15-year follow-up requirement with an overall sample size of 40 patients (14 in post-marketing setting, minimum 5-8 future commercial patients), providing milestone dates of final protocol submission by November 30, 2025, study completion by December 31, 2044, and final report submission by June 31, 2046, with an expected 18-year

*study duration and anticipated enrollment of 3 patients per year. Second, the applicant acknowledged FDA's sample collection and testing requirements, confirming inclusion of methods for 72-hour neoplasm reporting and detailed testing algorithms in their final protocol, while providing comprehensive malignancy workup procedures including immediate actions within 24 hours, mandatory sample collection requirements for peripheral blood, bone marrow, and tumor tissue, plus detailed follow-up monitoring protocols. Third, regarding study design, the applicant confirmed that their LTFU study fulfills the post-approval commitment study requirements by incorporating both clinical development and commercial patients without separate cohort divisions, stating that analysis and reporting by development phases will be possible while maintaining integrated oversight for this rare disease.*

*On July 31, 2025, FDA issued a PMR notification letter to the Applicant which included the following safety PMR "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 patients with Wiskott Aldrich Syndrome (WAS) who received treatment with etuvetidigene autotemcel. The study will include 14 patients with WAS who received etuvetidigene autotemcel and each enrolled patient will be followed for 15 years after product administration. The anticipated milestone dates as above were included in this notification letter.*

## **7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN**

### **7.1 Important Identified Risks**

The Applicant states that there are no important identified risks for Telethon003.

The Applicant acknowledges risks related to medical and surgical procedures (central line placement, leukapheresis), mobilizing agents, and pretreatment and conditioning regimens required for Telethon003 administration. Since these are part of the treatment process and not specifically related to Telethon003, the Applicant does not consider them important identified risks of Telethon003.

Risks associated with mobilizing agents, pretreatment, and conditioning will be managed in clinical practice through patient monitoring and standard of care per the respective product prescribing information. Risks related to medical/surgical procedures will be monitored in clinical practice using routine pharmacovigilance.

**Reviewer Comments:** *The Applicant proposes to monitor risks related to medical and surgical procedures, mobilizing agents, pretreatment, and conditioning regimens primarily through routine pharmacovigilance (signal detection and adverse event reporting). Furthermore, risk minimization information related to these risks will be included in the prescribing information. Since these risks are related to the treatment process rather than Telethon003 itself, the proposed plan is considered adequate.*

### **7.2 Important Potential Risks**

#### **7.2.1 Malignancy due to insertional oncogenesis**

Lentiviral vector integration into the human genome carries a theoretical risk of oncogene activation. The Applicant addresses this concern on page 42 of the PVP by stating that their use of self-inactivating (SIN) lentiviral vectors with minimal enhancer activity mitigates the theoretical risk of malignancy due to insertional oncogenesis. With newer generation lentiviral

vectors, no leukemogenesis has been observed in gene therapy trials involving hematopoietic stem cell genetic modification.<sup>9</sup> In the clinical safety data reviewed for this BLA, one serious adverse event of papillary thyroid cancer occurred in the EAP-HE; however, vector copy number analysis showed no viral gene sequences within thyroid tumor cells, and this event was considered unrelated to Telethon003 by the treating physician. No reports of leukemia or lymphoma were reported among any participants during long-term monitoring.

To address this safety concern, the applicant has proposed monitoring in ongoing studies and a study to monitor the long-term safety of Telethon003 up to 15 years after treatment, as well as via routine pharmacovigilance activities including the commitment to submit expedited (15-day) reports to FAERS for all malignancies, regardless of seriousness of the event or label status.

Additionally, the proposed package insert (BLA 125846.0) contains a Warnings and Precautions subsection (5.7) that outlines the theoretical risk of leukemia or lymphoma following Telethon003 treatment and provides guidance for management should a case be identified. The applicant further notes on page 61 of the PVP that "the management of the potential risk of malignancy due to insertional oncogenesis is included in the Healthcare professionals' educational materials and will be included in the LTFU protocol."

**Reviewer Comment:** *The Applicant's proposed pharmacovigilance activities are adequate to assess malignancy due to insertional oncogenesis following treatment with Telethon003.*

### 7.3 Important Missing Information

#### 7.3.1 Long Term Safety

The median follow-up duration in the Integrated Safety Summary (N=27) was 5.7 years; however, genetically modified cells persist lifelong, and with Telethon003 use in larger populations, potential gene-related delayed adverse events could emerge.

To address this missing information, the Applicant plans to utilize routine pharmacovigilance, educational materials, clinical studies, and programs and the proposed LTFU study to monitor and identify delayed adverse events and serious adverse events.

**Reviewer Comment:** *The Applicant's proposed pharmacovigilance activities are adequate to assess the long-term safety of Telethon003.*

## 8 DPV ASSESSMENT

The clinical safety data submitted in support of this application is limited by small sample sizes and lack of a control group, which reduces the likelihood of detecting rare but serious AEs and limits our ability to assess causality for observed AEs. Notwithstanding these limitations, and considering that WAS is a rare disease, we conclude that review of Applicant-submitted safety data adequately describes the safety concerns of WASKYRA in the submitted pharmacovigilance plan and the proposed actions. Many of the reported SAEs were considered related to conditioning, immunosuppression, and study procedures. The safety concerns identified with the use of WASKYRA were appropriately included as important risks in the proposed Pharmacovigilance Plan (PVP). One fatal event identified was not considered related to WASKYRA; however, conditioning and an underlying disease could not be excluded. WASKYRA is not approved for marketing in any country, therefore no postmarketing safety data was available for review. Considering the available safety data and its limitations, this reviewer concluded that the Applicant's proposed PVP (STN 125846/0.21, received on July 18, 2025) is acceptable.

The CBER Surveillance Program (CSP) team conducted an *Active Postmarket Risk Identification and Analysis (ARIA)* assessment for Waskyra under FDAAA section 901. On June 9, 2025, it was determined that the BEST system is incapable of evaluating the serious risks of secondary malignancy and long-term safety outcomes, necessitating a post-market requirement (PMR) study. The Applicant was informed on July 9, 2025, that their proposed Post Authorization Safety Study (PASS) would be classified as a PMR. In response, the Applicant agreed to implement enhanced pharmacovigilance for reporting secondary malignancies.

## **9 DPV RECOMMENDATIONS**

Should this original BLA be approved, OBPV/DPV has the following recommendations for postmarketing safety monitoring of WASKYRA:

1. Routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80.
2. Submission of expedited (15-day) reports for secondary malignancies regardless of seriousness of the event or label status.
  - a) In the periodic safety reports, provide aggregate safety assessments (based on interval and cumulative postmarketing safety data) for the risk of all secondary malignancies. In their assessments, specify data sources for reports of secondary malignancies, i.e., clinical trial data, or data from postmarketing safety study(ies), or data from postmarketing spontaneous reports.
  - b) Include a summary of any available interim reports, as applicable, for your ongoing long term follow up (LTFU) postmarketing safety study(ies) to assess the serious risk of secondary malignancies occurring after treatment with WASKYRA.
- 3) Require as a Postmarketing Requirement (PMR) study: A postmarketing, prospective, observational study to assess and characterize the risk of secondary malignancies and long-term safety following treatment with WASKYRA (for additional details, see the PMR Notification letter sent July 31, 2025).

The Office of Therapeutics Products (OTP) clinical review team and the DPV pharmacovigilance review team agree that the existing safety data does not justify implementing a Risk Evaluation and Mitigation Strategy (REMS) for this product. Additionally, no postmarketing commitment (PMC) for a safety study has been proposed.

**APPENDIX**  
**Materials Reviewed**

**Table A1: Materials reviewed in support of this assessment**

<b>Date</b>	<b>Source</b>	<b>Document Type</b>	<b>Document(s) Reviewed</b>
December 10, 2025	Fondazione Telethon ETS	125846/0	Module 2.7.4 Summary of Clinical Safety
January 10, 2025	Fondazione Telethon ETS	125846/0.1	1.16.1 Risk Management Pharmacovigilance Plan (Non-REMS)
December 10,2024	Fondazione Telethon ETS	125846/0	Module 2.5 Clinical Overview
January 10, 2025	Fondazione Telethon ETS	125846/0.1	Module 5.3.5.4 Clinical Study Reports
December 10,2025	Fondazione Telethon ETS	125846/0	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (OTL-103-4)
December 10,2025	Fondazione Telethon ETS	125846/0	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (TIGET-WAS)
December 10, 2024	Fondazione Telethon ETS	125846/0	Module 5.3.5.3 Integrated Summary of Safety
January 10, 2025	Fondazione Telethon ETS	125846/0.1	Module 1.14.1.3 Draft Label text
January 10, 2025	Fondazione Telethon ETS	125846/0.1	Module 5.3.5.4 Other study Reports; Albert (WAS worldwide patients outcomes survey report), 2052030 (EAP for Hematopoietic stem cells), Pallas systematic literature review on outcomes among WAS patients, Valle (WAS): Study WAS patients), WAS-648-96



Date	Source	Document Type	Document(s) Reviewed
December 10, 2025	Fondazione Telethon ETS	125846/0	Module 5.3.5.2 A Long-term Follow-up Study for Subjects Previously Treated with Autologous ex vivo Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy for Wiskott-Aldrich Syndrome (WAS) WAS TLT003-01)- Clinical Protocol
July 18, 2025	Fondazione Telethon ETS	125846/0.21	Module 1.16.1 Risk Management Plan (Non-REMS) Pharmacovigilance plan for WASKYRA
June 25,2025	Fondazione Telethon ETS	125846/0.19	1.11.3 Clinical Information Amendment- Response to DPV IR #1 dated June 25,2025
July 18, 2025	Fondazione Telethon ETS	125846/0.21	1.11.1 Clinical Information Amendment – Response to DPV IR # 2 dated July 11, 2025,

**Table A2: DPV Information Requests (IRs)**

IR #	Date IR was sent	IR Description	Sponsor response received Date	STN
DPV IR #1	June 25,2025	Clarification and feedback on post-authorization safety study; request for enhanced pharmacovigilance for secondary malignancies	June 25,2025	BLA 125846/0.19
DPV IR #2	July 11,2025	Clarification and feedback on the 15-year postmarketing observational study for Waskyra to monitor long-term safety and secondary malignancies, with enhanced pharmacovigilance including expedited malignancy reporting, tumor specimen analysis protocols, and updated safety monitoring plans.	July,16 and 18,2025	BLA 125846/0.21

Abbreviations: Division of Pharmacovigilance (DPV), Information Request (IR), submission tracking number (

## References

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- <sup>1</sup> Malik, M.A. and M. Masab, *Wiskott-Aldrich Syndrome*, in *StatPearls*. 2024
- <sup>2</sup> Burns, S., et al., Mechanisms of WASP-mediated hematologic and immunologic disease. *Blood*, 2004. 104(12): p. 3454-62.
- <sup>3</sup> [Wiskott-Aldrich syndrome/X-linked thrombocytopenia: WASP gene mutations, protein expression, and phenotype - PubMed](#)
- <sup>4</sup> Malik, M.A. and M. Masab, *Wiskott-Aldrich Syndrome*, in *StatPearls*. 2024: Treasure Island (FL).
- <sup>5</sup> [Risks Associated With Lentiviral Vector Exposures and Prevention Strategies - PMC](#)
- <sup>6</sup> [BUSULFAN - Pharmaceuticals - NCBI Bookshelf](#)
- <sup>7</sup> [Wiskott–Aldrich syndrome: diagnosis, current management, and emerging treatments - PMC](#)
- <sup>8</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products>
- <sup>9</sup> [Clinical use of lentiviral vectors | Leukemia](#)