

| | |
|--|--|
| Application Type | BLA |
| STN | 125846 |
| CBER Received Date | January 10, 2025 |
| PDUFA Goal Date | December 10, 2025 |
| Division / Office | CBER/OTP/OCE/DCEGM/GMB2 |
| Committee Chair | Laura DeMaster, Ph.D. |
| Clinical Reviewer(s) | Gumei Liu, M.D., Ph.D. |
| Project Manager | Cecilia Crowley, B.S. |
| Priority Review | Standard |
| Reviewer Name(s) | Freda Cooner, Ph.D. OBPV/DB/TEB1 |
| Review Completion Date / Stamped Date | December 3, 2025 |
| Supervisory Concurrence | Tingting Zhou, Ph.D., Team Leader OBPV/DB/TEB1 |
| | Boguang Zhen, Ph.D., Branch Chief OBPV/DB/TEB1 |
| | John Scott, Ph.D., Division Director OBPV/DB |
| Applicant | Fondazione Telethon ETS (FTE) |
| Established Name | Telethon 003 (formerly OTL-103 and GSK2696275) |
| (Proposed) Trade Name | WASKYRA |
| Pharmacologic Class | (etuvetidigene autotemcel) Autologous CD34 ⁺ Cells Transduced with Lentiviral Vector |

| | |
|---|--|
| | Expressing Human Wiskott-Aldrich Syndrome Gene |
| Formulation(s), including Adjuvants, etc | Cryopreserved dispersion for infusion |
| Dosage Form(s) and Route(s) of Administration | 50 mL (nominal volume) ethylene vinyl acetate (EVA) infusion bag (or multiple bags) at a target concentration of $2 - \text{[REDACTED]}^{(b)(4)} \times 10^6$ viable cells per mL, in a volume of 10 to 20 mL of cryopreservation medium per EVA bag |
| Dosing Regimen | $2 - \text{[REDACTED]}^{(b)(4)} \times 10^6$ cells/mL dispersion for infusion |
| Indication(s) and Intended Population(s) | 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 |

1. Executive Summary

Fondazione Telethon ETS is submitting this marketing application seeking to obtain approval of the advanced therapy medicinal product referred to as Waskyra (Telethon003) for the treatment of Wiskott-Aldrich syndrome (WAS). Telethon003 is a gene therapy containing an autologous CD34⁺ cell enriched population that contains hematopoietic stem and progenitor cells (HSPCs) transduced *ex vivo* using a lentiviral vector encoding the human *WAS* gene.

The Telethon003 clinical development program comprises two clinical studies (Study 201228 and Study OTL-103-4) and an Expanded Access Program (EAP), consisting of a Hospital Exemption (HE) and a Compassionate Use Program (CUP). At the time of the data cut for the integrated efficacy and safety analyses for this application, 18 participants had been treated in the two clinical studies. In addition, nine participants had been treated in the EAP. At the time of analysis, 27 participants had been treated with Telethon003, with a follow-up ≥ 8 years for eight of these participants and greater than one year in all but one participant. The participants included in the analysis all received treatment at a single site in Italy except for one that was treated at a clinical site in the United States to allow the treatment of additional participants with the intended commercial cryopreserved formulation.

Based on the integrated analysis, all but one participant survived until the end of the trial or the data cut. The two endpoints of interest are severe infections and moderate to severe bleeding episodes. The rate of severe infections decreased from 2.0 (95% confidence interval [CI]: 1.50, 2.61) infections per person-year of observation (PYO) in the 12-month period before treatment to 0.2 (95% CI: 0.04, 0.40) infections per PYO in the 6-18-month period post-Telethon003. The rate of moderate to severe bleeding events decreased from 2.0 (95% CI: 1.50, 2.61) events per PYO in the year before Telethon003 infusion to 0.8 (95% CI: 0.49, 1.22) events per PYO in the 12 months following Telethon003 and 0.03 (95% CI: 0.003, 0.099) events per PYO in the >4-year period.

Both clinical trials were designed as exploratory safety studies. Thus, all data in the Telethon003 clinical development program submitted for efficacy evaluation were collected through adverse event (AE) case report forms (CRF) following routine safety assessment schedules as opposed to more rigid efficacy data collection. Furthermore, a large portion of the pre-treatment data were collected retrospectively which caused irreconcilable data issues including missing data. Finally, there was no pre-specified statistical hypothesis testing and all analyses are presented descriptively. Therefore, I defer to the clinical team on the approval recommendation based on the overall benefit-risk assessment and considerations of unmet medical need.

2. Clinical and Regulatory Background

Wiskott-Aldrich syndrome (WAS) caused by mutations in the *WAS* gene, is a rare X-linked primary immune deficiency characterized by microthrombocytopenia and associated bleeding, eczema, recurrent infections, increased susceptibility to develop

autoimmunity and lymphoreticular malignancies. It has an overall incidence estimated between 1/100,000 and 1/1,000,000 live male births. WAS is a life-threatening illness associated with a severely reduced life expectancy. Current treatment options consist of conventional symptomatic and preventive management and allogeneic hematopoietic stem cell transplantation (HSCT), which is considered the only potentially curative treatment for WAS.

Fondazione Telethon is developing Telethon003, an autologous gene therapy product manufactured from CD34⁺ cells transduced with lentiviral vector (LVV) expressing human *WAS* gene. Telethon003 is formulated in media containing dimethyl sulfoxide (DMSO) and cryopreserved for storage in the vapor phase of liquid nitrogen until administration.

Telethon003 was originally developed out of the partnership between Ospedale San Raffaele (OSR) and Fondazione Telethon through their joint venture San Raffaele Telethon Institute for Gene Therapy (SR-TIGET). In November 2013, GlaxoSmithKline plc (GSK) exclusively in-licensed the gene therapy program for WAS from SR-TIGET. During the time GSK owned the rights for the investigational product (GSK2696275, also referred to as OTL-103 and currently known as Telethon003), a pre-IND meeting was conducted in May 2017 with the FDA on clinical and nonclinical aspects of Telethon003 development for the treatment of WAS. Subsequent to the pre-IND meeting, Orchard Therapeutics acquired the rights of the program from GSK in April 2018 and became the sole financially responsible sponsor. In March 2022, Orchard Therapeutics announced their intention to discontinue investment into certain assets for primary immunodeficiencies, including OTL-103, now known as Telethon003. The product, Telethon003, was returned to Fondazione Telethon and all INDs with associated designations transferred to Telethon as of October 2023.

GSK had several communications with the Office of Tissues and Advanced Therapies (OTAT), in particular a pre-IND Written Response Meeting (PTS# PS003228) in May 2017. During this meeting, a sample size of 8 in the initial phase 1/2 study, TIGET-WAS (201228), was proposed and the FDA feedback was, “based on the rarity of WAS, the size of the safety database, including the length of follow-up, the study may suffice.” The FDA urged the sponsor to provide historical data for formal comparisons of at least the major efficacy outcome variables and comprehensive medical histories for all enrolled participants.

A Type B pre-BLA meeting was held on November 13, 2024, where FDA agreed on the general contents of this BLA submission but noted that the adequacy of data to support a BLA for the proposed indication would be a review issue.

3. Statistical Evaluation

Due to the small sample size and similarity in data collection and representation across the Telethon003 clinical development program, this review will focus on integrated analysis with all data from both clinical trials and EAP.

The Telethon003 clinical development program comprises two clinical studies (TIGET-WAS and OTL-103-4) and a completed Expanded Access Program (EAP), consisting of a Hospital Exemption (HE) and a Compassionate Use Program (CUP). The two clinical studies, study TIGET-WAS (also known as Study 201228, in which a fresh formulation of Telethon003 was used) and study OTL-103-4 (in which a cryopreserved formulation of Telethon003 was used), are non-randomized, single arm, open-label, prospective studies in participants with WAS. Study TIGET-WAS (201228) was entitled “A phase I/II clinical trial of hematopoietic stem cell gene therapy for the Wiskott-Aldrich Syndrome.” It was a single-arm, single-center study with the first participant enrolled on April 20, 2010 and the last (eighth) on February 26, 2015. The first participant was treated on June 11, 2010 and the last on September 11, 2015. Study OTL-103-4 was entitled “A Single Arm, Open Label Clinical Study of Haematopoietic Stem Cell Gene Therapy with Cryopreserved Autologous CD34⁺ Cells Transduced with Lentiviral Vector encoding WAS cDNA in Subjects with Wiskott-Aldrich Syndrome (WAS).” The first participant was treated on April 11, 2019.

In each study, the stem cell harvest for drug product manufacture occurred on a date tailored to each participant’s condition and clinical needs. The harvest was planned to allow sufficient time for safety testing for product release to take place prior to administration of the drug product. Rituximab was administered to the participant at day - 22. All participants treated with Telethon003 were to be monitored for up to 8 years in study TIGET-WAS and for up to 15 years in study OTL-103-4 post-treatment.

Both studies were originally designed to evaluate safety of the treatment. After multiple discussions with the FDA, the sponsors added efficacy objectives to the studies, using the 12-month pre-treatment period as comparator for clinical efficacy endpoints of annualized rates of severe infections and moderate to severe bleeding episodes. The EAP also had a similar design and used the 12-month pre-treatment period as comparator for clinical efficacy endpoints of annualized rates of severe infections and moderate to severe bleeding episodes.

Participants were enrolled into the two clinical studies and protocols under the EAP between April 2010 and March 2022. Study TIGET-WAS and the EAP were completed by November 2023, and the data cut for study OTL-103-4 was December 4, 2023. Efficacy data from the TIGET-WAS and OTL-103-4 studies and the EAP have been integrated in the present summary in order to assess the clinical efficacy of Telethon003 in a combined analysis. No formal comparison of results within each study or across the studies was conducted.

3.1. Demographics and Baseline Characteristics

At the time of data cut, study TIGET-WAS, study OTL-103-4 and the EAP had completed Telethon003 dosing and enrollment was closed. Study TIGET-WAS and the EAP were closed, with any remaining participant visits, as scheduled in their respective protocols, transferred to long-term follow-up (LTFU) study. Study OTL-103-4 is ongoing. To date, a total of 28 participants have been enrolled, with data collected from

27 participants treated across the Telethon003 clinical development program. The participant enrolled but not treated was from EAP/CUP, who was a male white patient aged 25 years when enrolled. Since there are limited data collected from this subject as medical history or during screening period, the description of summary and results in this section are based on data from the 27 treated participants only.

One EAP/HE adult participant, 35 years of age at treatment, died 4.5 months after Telethon003 infusion due to a deterioration of a pre-existing neurological condition. The 26 surviving participants had a follow-up range of 1.2 to 13.3 years, with 22 participants having completed 3 years, 15 participants having completed 5 years, eight participants having completed 8 years, and five participants having completed 10 years. All participants in study TIGET-WAS and the EAP completed the study and all participants in study OTL-103-4 remain on study.

All participants were male and the majority (20 [74.1%] participants) were white. Except for two participants in the EAP (27 and 35 years of age), all participants were under 18 years of age at the time of treatment. The age of participants at the time of treatment ranged from 11 months to 35 years, with 11 (40.7%) participants aged < 2 years, and 9 (33.3%) participants were aged \geq 5 years at the time of treatment.

The applicant claims that all participants were symptomatic at the time of enrollment, as demonstrated in the individual participant narratives. They all had thrombocytopenia. The applicant further claims 23 participants had eczema at baseline (from transient to severe). Prior to treatment with Telethon003, 11 participants experienced clinical manifestations of autoimmunity and nine participants experience clinical manifestations of autoinflammation. Based on the applicant's report, the WAS gene mutations were defined as Class I in five participants and Class II in the other 22 participants. These mutations were identified as severe in 22 participants and of unknown severity in the other five participants.

Baseline Zhu scores ranged from 2.0 to 5.0A. All participants had severe WAS; 25 participants had a Zhu score \geq 3.0 at baseline and the participant with a Zhu score of 2.0 was identified as having a severe WAS mutation. One participant in the EAP had a Zhu score of 5.0A at baseline; however, it was windowed to the treatment visit because it was assessed after the start of mobilization for PBSC collection.

Based on the adverse events (AEs) collected with sufficient data of toxicity grade and event dates, 24 participants experienced severe infections or moderate to severe bleeding events in the 12 months before the treatment. Separately, there were 54 severe infections in 19 participants and 54 moderate to severe bleeding events in a different subset of 19 participants within the 12 months before the treatment.

3.2. Analysis of Primary Endpoints

The efficacy endpoints proposed by the applicant and for this review are:

- Overall survival
- Rate of moderate and severe bleeding events in the first 12 months post-treatment

- Rate of severe infections from 6 to 18 months post-treatment

As stated earlier, only one participant died, having experienced a fatal serious adverse event (SAE) of neurological decompensation during the 0-6-month period after Telethon003 infusion. Therefore, the overall survival endpoint cannot be properly evaluated.

For the annualized rate of bleeding or infection events, the person years observation (PYO) is calculated as the total observation period across all subjects within the given study period. The observation end date is the end of study date defined as the earliest of date of subject withdrawal (discontinuation) from the study, date subject completed the study and death date; or the data cut date for subjects are ongoing at the interim analysis. The estimate of annualized rate is the observed number of events divided by PYO and an exact Poisson procedure based on chi-square quantiles is used for confidence interval (CI) derivation.

The number and rate of severe infections in the 12 months period before treatment was compared with that in the 6-18 months period following Telethon003. The first 6 months following Telethon003 infusion were not taken into account in view of the effects of the conditioning regimen, which the applicant claims disrupts the immune system and makes the participants more vulnerable to infection during this period, when the immune system is being re-established from the genetically corrected hematopoietic stem and progenitor cells (HSPCs; Telethon003). Participants experienced fewer severe infections in the 6-18 months period after Telethon003 infusion than in the 12 months period before the treatment.

The rate of severe infections decreased from 2.0 (95% CI: 1.50, 2.61) infections per PYO in the 12 months period before treatment to 0.2 (95% CI: 0.04, 0.40) infections per PYO in the 6-18-month period post-Telethon003. Three (11.1%) participants had more than five severe infections each in the 12 months period before treatment, whereas 16 participants had 1-5 severe infections in the same time period. In the 6-18-month phase post-Telethon003 infusion, no participants had more than five severe infections and nine (34.6%) participants experienced one or more severe infections during the entire follow-up phase following 6 months post-Telethon003 infusion. There was no notable difference in the pre- and post-treatment event rates between the two clinical studies, with 2.1 (95% CI: 1.2, 3.4) severe infections per PYO in the pre-treatment phase in study TIGET-WAS compared with 2.4 (95% CI: 1.54, 3.58) in study OTL-103-4, and 0.1 (95% CI: 0.0, 0.2) severe infections per PYO in the more than 6 months follow-up in study TIGET-WAS and 0.1 (95% CI: 0.01, 0.26) severe infections in study OTL-103-4. Note that the PYO exposure in study TIGET-WAS beyond 6 months is 82.4 years compared with 27.3 years in study OTL-103-4. The rate of severe infections in the EAP was slightly lower in the 12 months period before treatment, with 1.4 (95% CI: 0.8, 2.5) events per PYO; however, it was similar to the clinical studies in the post-treatment evaluation period starting at month 6 (0.1 events per PYO [95% CI: 0.0, 0.2]).

The majority of severe infections were Common Terminology Criteria for Adverse Events (CTCAE) Grade 3. Two CTCAE Grade 4 severe infections were reported in the first 6 months following Telethon003 infusion (bacterial sepsis and aspiration pneumonia), and one in the 2-3-year follow-up period (acute appendicitis). A total of 14 severe infections occurred after more than 6 months of follow-up.

The rate of moderate and severe bleeding events decreased from 2.0 (95% CI: 1.50, 2.61) events per PYO in the 12 months before treatment to 0.8 (95% CI: 0.49, 1.22) events per PYO in the 12 months following Telethon003 and 0.03 (95% CI: 0.003, 0.099) events per PYO in the more than 4 years period. When severity was analyzed separately, the rate of severe bleeding events decreased from 0.9 (95% CI: 0.57, 1.32) events per PYO in the 12 months before treatment to 0.08 (95% CI: 0.009, 0.274) events per PYO in the 12 months following Telethon003, and the rate of moderate bleeding events decreased from 1.1 (95% CI: 0.75, 1.59) events per PYO in the 12 months before treatment to 0.7 (95% CI: 0.43, 1.13) events per PYO in the 12 months following Telethon003. At more than 4 years post treatment, the rate of moderate and severe events decreased further to 0.03 (95% CI: 0.003, 0.099) events.

There were only four severe bleeding events in the entire post-treatment period, with two of these events taking place in the first 6 months after Telethon003 infusion. One of these was a severe post-treatment bleeding event of petechiae, which occurred in the first month post-Telethon003 in a participant. No Grade 4 bleeding events were reported in study TIGET-WAS and the EAP or up to the data cut of study OTL-103-4. The remaining two severe bleeding events occurred between 3 and 4, and more than 4 years post-treatment, respectively.

The rate of moderate bleeding events increased from 1.1 (95% CI: 0.75, 1.59) events per PYO in the 12 months before Telethon003 to 1.3 (95% CI: 0.74, 2.04) events per PYO in the first 6 months following Telethon003 infusion, and decreased thereafter to 0.2 (95% CI: 0.02, 0.55) events per PYO 6-12 month post-Telethon003 infusion, and 0.2 (95% CI: 0.12, 0.25) in the post-treatment phase as a whole.

3.3. Efficacy Conclusions

Overall, all participants treated with Telethon003 in the two clinical studies were alive at the data cut, however, one participant treated with Telethon003 in the EAP died as a result of a fatal SAE unrelated to Telethon003. A notable reduction was observed in the rate of severe infections and moderate to severe bleeding events.

4. Overall Conclusions and Recommendations

The clinical program for Telethon003 includes two clinical studies, both of which were designed and conducted as early phase studies with primary safety objectives. The efficacy results submitted in support of approval of this BLA were derived based on safety data collection procedures, which lack rigor for reliable efficacy analyses. In the study populations, the rates of severe infections and moderate to severe bleeding episodes decreased in the 6-18 months period after treatment compared to the 12 months prior to

treatment. However, without pre-specified hypothesis tests, the results presented do not have sufficient context to draw population inference and are descriptive observations only. Furthermore, the pre-treatment data, used as a comparator for post-treatment data evaluation, were collected retrospectively and have irreconcilable data issues including missing data. The study design and data collection preclude statistical conclusions being drawn. Therefore, I defer to the clinical team on the approval recommendation based on the overall benefit-risk assessment and considerations of unmet medical need.