



**Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)**

RWE EPIDEMIOLOGY CONSULT MEMORANDUM

Date: August 27, 2025

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Sponsor: Fondazione Telethon ETS (Rome Italy)/US Agent eCTD LLC

Product: etuvetidigene autotemcel Telethon003 (TL003)] or
WASKYRA Autologous CD34+ cell enriched population that
contains haematopoietic stem and progenitor cells (HSPC)
transduced ex vivo with a lentiviral vector encoding the human
Wiskott-Aldrich Syndrome (WAS) gene; IV administration.

Application Number: BLA 125846

Proposed Indication: Treatment of patients aged 6 months and older with severe
WAS who have a mutation in the WAS gene and for whom no
suitable HLA-matched related hematopoietic stem cell donor
is available.

Submission Date: January 10, 2025

Due Date: September 10, 2025

Executive Summary

etuvetidigene autotemcel Telethon003 (TL003)] or WASKYRA is an Autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells (HSPC) transduced ex vivo with a lentiviral vector encoding the human Wiskott-Aldrich Syndrome (WAS) gene administered as a single IV administration. This review evaluated two independent documents that were used to provide context for the clinical study data. These included the following:

- A worldwide survey of WAS patient outcomes, conducted by WAS expert Prof M. Albert from LMU Klinikum, Munich Germany.
- A systematic literature review on WAS patient outcomes.

These documents addressed the European Medicines Agency's (EMA) recommendation to present historical data from relevant populations. This approach aimed to rule out potential regression to the mean in outcome variables, particularly for patients who either would have received a matched unrelated donor hematopoietic stem cell transplant (MUD HSCT) or lacked a suitable donor.

The sponsor in their response to our information request for patient level data stated that the survey data were not meant to be used as primary evidence of effectiveness nor were they intended to be used for direct comparative analysis. In addition, the sponsor is not able to provide patient level data and therefore the survey outcomes cannot be compared to the clinical trial data.

This systematic review covering 702 patients addresses critical gaps in WAS natural history data and provides valuable insights which are useful for understanding the effectiveness of the new treatment. However, this study is not RWE and has significant limitations including potential duplicate patient entries and the lack of validated appraisal checklists which weakens its strength as supportive evidence of treatment effectiveness. In conclusion the Albert survey and the systematic review do not meet the criteria to provide real-world data and cannot be used as supportive evidence of treatment effectiveness nor can they be compared to data from the WAS clinical trials.

1. OBJECTIVE:

To evaluate the Real-World Evidence (RWE) in the Biologics License Application (BLA) for Telethon003.

2. BACKGROUND INFORMATION AND REGULATORY HISTORY

Table 1: Documents Reviewed

Amendment	Date IR sent	Date Amendment Received	Documents Reviewed
BLA 125846		01/10/2025	albert-survey-rpt
BLA 125846		01/10/2025	pallas-2022-rpt
BLA 125846	04/18/2025	01/10/2025	1-11-1-resp-to-ir14-28apr25
BLA 125846		01/10/2025	valle-2024-rpt.
IND (b) (4)		11/10/2024	Pre-BLA IND (b) (4)

Table 2: Key Dates and designations

Regulatory Milestone/Event	Date
Orphan Designation Granted	April 30, 2010
Pre IND meeting	May 2017
Rare Pediatric Disease Designation Granted	Dec 2017
RMAT Designation Granted	July 2019
IND 18919 submitted	May 15 2019
IND 18919 meetings	<ul style="list-style-type: none"> • March 2020 • Feb 2021 • June 2024
BLA 125846 Submitted	Jan 10, 2025
Action Due Date	Sept 10, 2025

3. SUMMARY OF STUDY DOCUMENTS

A. Background

Wiskott-Aldrich Syndrome (WAS) is a rare, X-linked primary immune deficiency and platelet disorder affecting 1 to 9 per 1,000,000 live male births. Characterized by thrombocytopenia, bleeding events, eczema, and recurrent or severe infections, WAS also increases the risk of autoimmune disorders and blood cancers. The disease is caused by mutations in the WAS gene, which encodes the Wiskott-Aldrich syndrome protein (WASP). Without curative intervention, WAS is life-threatening, with a median survival of just 14.5 years. The main causes of death are severe infections, hemorrhages, and malignancies. Current treatment options consist of conventional symptomatic and preventive management and allogeneic hematopoietic stem cell transplantation (HSCT), which can be disease stabilizing when successful. Autologous gene therapy (GT) can represent a valid alternative therapeutic option for patients lacking an HLA-related identical donor or for older patients for whom HSCT combined with fully myeloablative conditioning is considered too risky.

etuvetidigene autotemcel Telethon003 (TL003)] or WASKYRA is an Autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells (HSPC) transduced ex vivo with a lentiviral vector encoding the human WAS gene and is administered as a single IV infusion. Telethon003 has shown promising results in clinical trials (Table 3). The overall survival rate was 96.3% (95% CI: 82, 99%) in the integrated analysis from the clinical trials, 83.3% (95% CI: 80.4, 85.9%) reported in the systematic literature review and 80% (95% CI: 75-86%) from a patient survey (Table 4). These clinically meaningful benefits suggest that Telethon003 could potentially improve outcomes for patients with this rare and serious condition.

Table 3: Summary of Telethon003 Clinical Studies

	Amendment number	Study Title	Study Objectives	Study Dates	# of patients	Study Design
Integrated analysis	Study 201228 EudraCT: 2009-017346-32; NCT01515462 TIGET-WAS	A phase I/II clinical trial of hematopoietic stem cell gene therapy for the WAS (TIGET-WAS)	To assess the safety and efficacy of Telethon 003	04/10/2010-11/09/2023	8	Phase 1/2 single arm clinical study
	OTL-103-4 EudraCT: 2018-003842-18; NCT03837483	A single-arm, open-label clinical study of hematopoietic stem cell gene therapy with cryopreserved autologous CD34+ cells transduced with lentiviral vector encoding WAS cDNA in subjects with WAS	1. To evaluate the clinical efficacy of the cryopreserved formulation of Telethon003 at 12 months for moderate/severe bleeding events and from 6 to 18 months after treatment for severe infections. 2.To evaluate the safety and efficacy of the cryopreserved formulation	01/21/2019-12/04/2023	10	Phase 3 clinical study single-arm, open-label
	Expanded Access Program (EAP) eap-he-cup	Hospital Exemption (HE) 205030 – Hematopoietic Stem Cell Gene Therapy Telethon003 In Wiskott-Aldrich Syndrome (WAS) Patients	To provide treatment for patients affected by WAS with high unmet medical need in advance of the product being commercially available according to the Italian. D.M. 08/05/2003 and D.M. 16/01/2015	12/14/2015-10/17/2023	3	Prospective, single-center treatment program in patients with WAS.
		Compassionate Use Program (CUP) 206257			6	
	WAS-TLT003-01	A Long-term Follow-up Study for Subjects Previously Treated with Autologous ex vivo Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy for WAS		11/04/2024		Designed to collect safety and efficacy data from WAS patients previously treated with Telethon003 for 15 years from the gene therapy treatment.
Comparative analysis	Systematic review	Systematic literature review on outcomes among patients with Wiskott - Aldrich syndrome (WAS)	Systematic review and metanalysis	2005-2022		Evaluated WAS Patients for survival, graft failure, graft versus host disease (GvHD), platelet counts, platelet transfusions, bleeding events, infection, eczema, autoimmune disease, malignancies, hospitalization, QoL and patient reported Outcomes after HSCT, other treatment or no treatment.
	Survey	Wiskott-Aldrich Syndrome Worldwide Patient Outcomes Survey Report	Worldwide survey of treatment facilities of WAS patients to gain the burden of morbidity and mortality associated with WAS following currently available treatments	1990-2014		Evaluated as retrospective investigation using patient-level data

Table created by reviewer based on tables provided by the sponsor.

B. Real World Evidence (RWE) Study Rationale

Two independent documents were used to provide context for the clinical study data:

- A systematic literature review on WAS patient outcomes.
- A worldwide survey of WAS patient outcomes, conducted by WAS expert Prof M. Albert from LMU Klinikum, Munich Germany.

These documents addressed the European Medicines Agency's (EMA) recommendation to present historical data from the relevant population. This approach aimed to rule out potential regression to the mean in outcome variables, particularly for patients who either:

- Would have received a matched unrelated donor hematopoietic stem cell transplant (MUD HSCT), or
- Lacked a suitable donor.

Table 4: Contextualization of study outcomes from integrated analysis and comparative analysis*

	All Telethon003 studies (TIGET-WAS, OTL-10304) and EAP	WAS systematic Literature Review (Natural history) ^a	Worldwide patient survey (Patient reported outcomes) ^b
Survival post treatment			
Overall survival	96% (95% CI:82-99%)	83.3% (95% CI:80.4-85.9%)	80% (95% CI: 75-86%)
Survival By Donor Type			
MSD/MFD	N/A	88.9% (95% CI: 80.2-94%)	93% (95% CI: 85%-100%)
URD	N/A	85.3% (95% CI: 79.4-89.4%)	76% (95% CI: 68-85%)
UCB	N/A	73.9% (95% CI: 66.4 -80.2%)	81% (95% CI: 70-95%)
MMFD/haploidentical	N/A	73.1% (95% CI: 63.3-81.1%)	71% (95% CI: 54-92%)
Survival by treatment type			
<5 years	100% (95% CI: 82-100%)	94% (95% CI: 88%-97%)	82% (95% CI: 76-88%)
≥5 years	88.9% (95% CI:57-98%)	66% (95% CI:32-86%)	73% (95% CI: 61-87%)
Treatment related complications			
Graft Failure			
	0%	11%	0%
Acute Graft Vs Host Disease			
All grades		34.5 % (95% CI: 30.7-38.4%)	

*Table created by reviewer based on tables provided by sponsor.

^aPallas Literature review

^bAlbert Survey Report

MSD=matched sibling donor, MFD=matched family donor, URD=unrelated donor, UCB=umbilical cord blood, MMFD=mismatched related donor.

4. RWE REVIEW OF “ALBERT SURVEY REPORT: WISKOTT-ALDRICH SYNDROME WORLDWIDE PATIENT OUTCOMES SURVEY REPORT”

4.1 Objective

This review aims to evaluate the suitability of the Albert survey as a comparator for Telethon003 clinical trials in the treatment of WAS patients.

4.2 Background Information

Professor Michael Albert designed an independent survey to enhance the understanding of the morbidity and mortality associated with WAS following currently available treatments. The survey retrospectively collected patient data from physicians at clinical centers with expertise in the management of patients with primary immune deficiencies. It focused on 1) survival outcomes and therapy-related complications. This data collection was designed to provide a comprehensive view of WAS patient outcomes across different treatment approaches, serving as a potential benchmark for comparing new therapies like Telethon003.

4.3 Data Collection

The survey data collection process was designed with the following key features: 1) Retrospective approach: data were collected on patient experiences and outcomes. 2) pseudo-anonymization: submitting physician ensured patient data was partially anonymized to protect privacy while maintaining necessary clinical information, as described in the Project Plan. 3) Global Reach: The survey targeted physicians from clinical centers worldwide with expertise in the management of WAS patients. 4) Distribution methods: Survey collection forms were sent directly to major centers treating patients with primary immunodeficiency diseases (PIDs). Electronic distribution was facilitated by the European Society of Immune Deficiencies (ESID).

4.4 Statistical Methods

Information on the occurrence of serious clinical events, including bleeding, infection, autoimmunity, and malignancy was collected and analyzed. For constructing Kaplan-Meier curves, only the first event in each event category was considered; all subsequent events in the same category were not included. Kaplan-Meier survival estimates were compared using the log-rank test. Kaplan-Meier curves for different events were factored in only for the first event of the specified category and were adjusted for competing risks. No adjustment has been made to adjust to the number of tests being conducted in the analyses. Mean incidences per patient-year were calculated for different times.

4.5 Relevant Results

The Patient Outcomes Survey Report for WAS analyzed data from 577 patients across 51 centers in 26 countries from 1990 to 2014. Key findings include:

1. Study Scope:
 - 577 patients from 51 centers in 26 countries
 - study period:(1990 to 2014)
 - Largest global dataset on WAS patients to date.
2. Patient Demographics:
 - 48.2% European, 19.6% USA patients
 - Median age at diagnosis: 1.5 years
 - 57.3% diagnosed within 2 years of birth, 79.2% within 5 years.
3. WAS Gene Mutations:

- All 577 patients had documented mutations.
- Most common: missense (45.5%), intronic variants (17.1%), nonsense (15.2%)
- 4. Treatment:
 - 45.6% received supportive (non-definitive) treatment.
 - 44.2% received HSCT (mostly MUD in Europe and USA)
 - 13.7% underwent splenectomy.
 - 2.4% received experimental gene therapy.
- 5. Age at First Procedure:
 - Median: ~2.3 years (3 years in USA)
 - 82.8% of HSCT recipients were under 5 years old.
- 6. Treatment Timeline:
 - 70% of first procedures occurred from 2000 onwards.
 - 75% of HSCTs performed before 2010.
- 7. Survival Outcomes:
 - 80.4% alive at time of survey
 - 10-year post-HSCT survival: 80% overall
 - 93% for MSD HSCT
 - 76% for MUD HSCT
 - Higher survival in patients ≤5 years at HSCT (82%) vs. >5 years (73%)
- 8. Causes of Death:
 - 19.6% (113/577) deceased
 - Main causes: infections (27.2%), bleeding (22.8%), HSCT-related events (15.8%)
- 9. Serious Clinical Events:
 - 15-year event-free survival: 33%
 - Median age at first serious event: 5.0 years
 - 55.8% experienced a serious event before first procedure.
 - 93.8% of initial serious events occurred before age 15.

This survey provides comprehensive data on WAS patient outcomes, highlighting the disease's early onset, treatment patterns, and the significant risks of serious clinical events and mortality associated with the condition.

5. REVIEW OF SYSTEMATIC REVIEW

Title: Systematic literature review on outcomes among patients with Wiskott-Aldrich syndrome (WAS)

5.1 Study Rationale:

Hematopoietic Stem Cell Transplantation (HSCT) is the primary recommended treatment for WAS patients with a Zhu score ≥ 3 who have a suitable donor. Alternative treatments include intravenous immunoglobulin therapy (IVIG), anti-infective prophylaxis, splenectomy, platelet transfusions, and thrombopoietin receptor agonists (TPO-RA). These alternatives aim to reduce infections, increase platelet counts, and prevent bleeding. A comprehensive review of WAS patients evaluated various outcomes post-treatment, including survival rates, graft-related complications, hematological improvements, disease-specific symptoms, and quality of life measures. This review analyzed data from 96 studies published between 2005-2021, focusing on survival, complications, and clinical outcomes after HSCT and other treatments.

5.2 Study Objectives:

The following outcomes were defined for the different treatment outcomes.

- 1) Overall survival following HSCT/other treatment/no treatment.
- 2) Frequency of graft versus host disease (GVHD) and graft failure post-HSCT.
- 3) Platelet counts post HSCT/other treatment/no treatment.
- 4) Platelet transfusions after HSCT/other treatment/no treatment.
- 5) Frequency of bleeding events post HSCT/other treatment/no treatment.
- 6) Frequency and type of infections that may have occurred post HSCT/other treatment/no treatment.
- 7) Eczema after HSCT/other treatment/no treatment.
- 8) Frequency of autoimmune diseases post HSCT/other treatment/no treatment.
- 9) Frequency of malignancies post HSCT/other treatment/no treatment.
- 10) Frequency of hospitalization post HSCT/other treatment/no treatment.
- 11) Patient reported outcomes/quality of life (QOL) after HSCT/other treatment/no treatment.

5.3 Study Design

This was a systematic review of literature conducted using PubMed and EMBASE

Reviewer comment: *The systematic review does not qualify as real-world evidence (RWE) according to the FDA's 2018 Framework for Real World Evidence Program. Real-World Data (RWD) are defined as data on patient health status or healthcare delivery routinely collected from various sources. Real-World Evidence (RWE) is the clinical evidence derived from analyzing RWD, showing the usage, benefits, or risks of a medical product.*

Although the systematic review is not RWE, it serves an important purpose:

1. *It synthesizes existing evidence, including RWE, to provide a comprehensive overview of treatment outcomes for WAS patients.*
2. *The review covers data from 1983 to 2016.*
3. *It includes a meta-analysis of treatment outcomes for 702 patients.*

This systematic review, therefore, while not RWE, incorporates and analyzes RWE along with other forms of evidence to offer insights into WAS treatment outcomes over a significant period.

5.4 Methods:

Study Population:

A total of 5,202 articles were retrieved of which 96 were identified as reporting data on patient outcomes in WAS patients after HSCT, Other treatments or no treatments.

Study Inclusion criteria:

- Data relevant for the objectives.
- All ages.
- Treated with HSCT, otherwise treated, or not treated.

Study Exclusion criteria:

- Articles that describe non-pertinent publication types (e.g. letters to the editor, editorials or comments, conference abstracts)
- Modelling studies that do not provide original data.
- Outcomes following HSCT not stratified for WAS patients (i.e. only combined in number with PID)
- Outcomes not stratified for WAS patients (i.e. only combined in number with PID)

5.5 Study Quality Assessment

A short quality assessment was performed for the articles that were selected for data-extraction. The nature of the studies relevant for the review objectives did not fit one of the validated checklists such as those from Cochrane collaboration, SIGN (Scottish Intercollegiate Guidelines Network), or GRADE (Grading of Recommendations Assessment, Development and Evaluation). These validated checklists are designed for critical appraisal of systematic reviews/meta-analysis, cohort studies, case control studies, diagnostic studies, and economic evaluations. The studies included in this review contained follow-up data of a group of WAS patients without using one of the above-mentioned study designs. The included articles were assessed on the setting, representativeness of individuals captured in the study and applied case definitions.

Reviewer comments:

The inability to use validated checklists for this review presents several challenges:

1. *Reduced strength of evidence: As noted, the lack of standardized assessment tools weakens the overall strength of the evidence.*
2. *Limited comparability: The unique assessment approach makes it difficult to compare these findings with other studies or meta-analyses.*
3. *Potential for bias: Without standardized criteria, there's an increased risk of subjective interpretation in the quality assessment.*
4. *Incomplete evaluation: The tailored approach might miss critical aspects of study quality that standard checklists are designed to catch.*
5. *Replication difficulties: Other researchers may find it challenging to replicate or validate this quality assessment process.*

However, it is important to note that this review does provide value by:

- *Filling a gap in the literature by synthesizing natural history data not otherwise available.*
- *Offering insights into Wiskott-Aldrich Syndrome outcomes that might not be captured by more rigid assessment methods.*

While the approach has limitations, it represents a pragmatic attempt to evaluate and synthesize important data that does not fit neatly into conventional research designs. This expanded summary provides a more balanced view of both the weaknesses and the potential value of the approach used in the review.

5.6 Data Extraction

Data extraction was done in Excel.

5.7 Pooled Analysis

Despite initial efforts to remove duplicate citations during the selection process in the systematic review, some patients were still included in multiple publications. This occurred for two main reasons: 1) researchers publishing updated analyses as their studies progressed and 2) patients being included in both single-site study reports and larger multi-center reviews. To address this issue, a thorough de-duplication process was implemented. This involved carefully examining the full texts of selected studies, focusing on treatment centers, study periods, patient characteristics, and transplant procedure details. This additional step allowed the identification of unique patients for various analyses, resulting in the following sample sizes: overall survival (n=702), survival by donor type (n=506), graft failure (n=438), frequency of GvHD (n=580), platelet counts (n=153), rate and types of infections (n=178), autoimmunity (n=312), and malignancy (n=305). This meticulous approach ensured that the data used in the analysis accurately represented individual patient outcomes without duplication.

Reviewer comments:

The authors' approach to handling potentially duplicate patient data has several notable weaknesses:

- 1. Uncertainty in patient uniqueness: Despite efforts to ensure the 702 patients were unique, this cannot be guaranteed without access to patient-level data. The same patient may appear in multiple studies, particularly in more recent publications that likely include previously reported data. This affects the relevance of the included patients, and we cannot be certain that these patients are similar to those studied in the WAS clinical trials.*
- 2. Limitations of non-interventional studies: Most included studies are non-interventional, the inference(s) drawn may be incorrect if based on estimates that are affected by confounding or other forms of bias. This impacts the reliability of study findings since the data are subject to confounding and biases.*
- 3. Inconsistency across studies: The authors highlight inconsistencies among the included studies, further weakening the overall strength of evidence.*
- 4. Potential for bias: The process of identifying and removing duplicates may introduce unintended bias, especially without a standardized method.*
- 5. Incomplete information: Some studies may lack sufficient details to definitively identify duplicates, leading to potential over- or under-estimation of unique patients.*
- 6. Loss of longitudinal data: Removing duplicates might result in losing valuable information about patient progress over time.*
- 7. Varying sample sizes: The inconsistent sample sizes for different outcomes (e.g., 702 for overall survival, 153 for platelet counts) may complicate drawing comprehensive conclusions.*
- 8. Replication challenges: The exact de-duplication process may be difficult for other researchers to replicate precisely.*

While the authors have made efforts to address these issues, the limitations inherent in the available data and the chosen methodology impact the overall strength of the evidence. This underscores the challenges in synthesizing data from multiple observational studies, particularly when dealing with rare diseases like Wiskott-Aldrich Syndrome.

5.8 Study outcomes

- i. **Survival post HSCT:**
 - a. Overall survival rate: 83.3% (95% CI: 80.4-85.9%) based on pooled analysis of 702 patients.
 - b. Survival improved from 75% pre-2000 to 89-91% post-2000.
 - c. IVIG treatment: 47.4% survival rate
 - d. thrombopoietin receptor agonist (TPO-RA) or IL-2 treatment: 100% survival in small studies
 - e. Survival varied by donor type: 88.9% for matched sibling/related donors, 85.3% for unrelated donors, 73.9% for cord blood, 73.1% for mismatched/haploidentical donors.
- ii. **Graft failure:**
 - a. 11% failure rate (438 patients)
 - b. Higher rates with haploidentical/mismatched family donors
- iii. **Graft versus host disease (GvHD):**
 - a. Acute GvHD: 34.5% (95% CI: 30.7-38.4%)
 - b. Chronic GvHD: 14.1% (95% CI: 11.5-17.2%)
- iv. **Platelet count:**
 - a. 81.7% of patients recovered normal platelet counts post-HSCT.
 - b. Variable responses to TPO-RA and IL-2 treatments
- v. **Platelet transfusions:**
 - a. 81.6% discontinued by day 35 post-HSCT.
 - b. 12.2% more discontinued by 18 months post-HSCT
- vi. **Bleeding events:**
 - a. Combined analysis showed that of 256 post HSCT patients, hemorrhage caused 8/45 deaths (17.8%) of post-transplant deaths.
 - b. 58% of IVIG-treated patients died from bleeding.
- vii. **Infections:**
 - a. 44.9% overall infection incidence post-HSCT (95% CI: 37.8-52.3%)
 - b. Infection types: 65% viral, 20% bacterial, 3.8% fungal, 1.3% parasitic, 7.5% unspecified

This summary provides an overview of the outcomes for various treatments of WAS, with HSCT showing generally positive results in terms of survival and platelet count recovery, but with notable risks of graft failure, GvHD, and infections. Outcomes have improved over time, but there remains a need for safer and more effective treatments for WAS.

6. INFORMATION REQUESTS

On 04/18/2025, an Information request was sent to the sponsor. The sponsor was asked to provide patient level data that were used in the data analysis for the Albert survey. Response was received 04/29/2025 in which Sponsor stated that there was no agreement to share patient-level data outside of Klinikum der Universitat Munchen (KUM, now known as university hospital of Ludwig Maximilian University of Munich (LMU Klinikum)), Munich, Germany for the protection of the privacy and confidentiality of the patients. Additionally, the sponsor clarified that the survey data were intended to provide the context of treatment outcomes of the natural course of WAS patients and not be used as a formal external comparator. The sponsor included the following in their response:

“The aggregated data from the Albert report have been included in the submission and are discussed in the Clinical Overview and Summary of Clinical Efficacy and Safety sections. These data are provided solely to offer context for the observed outcomes in patients treated with Telethon003 and to help describe the natural course of WAS in the absence of treatment. Importantly, the Albert data are not being used as primary evidence of effectiveness, nor are they intended for direct comparative analysis.”

7. DISCUSSION AND REVIEWERS' CONCLUSIONS

The Albert survey real-world study presents several concerns that warrant attention including, potential selection bias due to inclined responses from physicians who treated patients with favorable outcomes. Additionally, time-varying confounding since 1990-2014 period due to treatment advancements, challenges the relevance and comparability with the pivotal clinical trials. Additional issues involve the lack of control for confounding by indication, lack of patient-level data for reliable alignment with clinical trials, and potential responder bias favoring positive outcomes. The sponsor in their response to our information request for patient level data stated that the survey data were not meant to be used as primary evidence of effectiveness nor are they intended to be used for direct comparative analysis. In addition, the sponsor is not able to provide patient level data and therefore the survey outcomes cannot be compared to the clinical trial data.

The systematic review and meta-analysis of WAS patient outcomes following HSCT from the 1980's to 2016 offers a comprehensive synthesis of the treatment efficacy data, particularly for HSCT. This review covering 702 patients addresses critical gaps in WAS natural history data and provides valuable insights which are useful for understanding the effectiveness of the new treatment. While this study is not RWE, it may be relevant for evaluating treatments like Telethon003. Major limitations of the systematic review include potential duplicate patient entries and the lack of validated appraisal checklists which weakens its use as supportive evidence of treatment effectiveness.

Despite these limitations, both the systematic review and the Albert survey provides a foundation for evaluating new treatments and contributes to understanding WAS outcomes in the real-world settings. In conclusion the Albert survey and the systematic review do not meet the criteria to provide real-world data and cannot be used as supportive evidence of treatment effectiveness nor can they be compared to data from the WAS clinical trials.

APPENDIX I

RWE Guidances

1. [Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products](#)
2. [Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products](#)
3. [Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products](#)
4. [Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products](#)
5. [Data Standards for Drug and Biological Product Submissions Containing Real-World Data](#)
6. [Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products | FDA](#)
7. [Use of Electronic Health Records in Clinical Investigations](#)
8. [Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices](#)
9. [Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products | FDA](#)
10. [Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products | FDA](#)
11. [Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice | FDA](#)