

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

BLA Clinical and Clinical Pharmacology Review Memorandum

Application Type	351(a) original BLA
STN	125846
CBER Received Date	01/10/2025
PDUFA Goal Date	12/10/2025
Division / Office	CBER/OTP/OCE/DCEGM/GMB2
Priority Review (Yes/No)	Yes
Clinical Reviewer	Gumei Liu, MD, PhD CBER/OTP/PSPS
Clinical Pharmacology Reviewer	Xing Jing, PhD CBER/OTP/OCE/DCEGM/GMB1
Acting Clinical Pharmacology Team Leader	Xiaofei Wang, PhD CBER/OTP/OCE/DCEGM/GMB2
Labeling Reviewer Acting Associate Director for Labeling	Afsah Amin, MD, MPH CBER/OTP/OCE
Review Completion Date / Stamped Date	12/9/2025
Supervisory Concurrence Branch Chief	Rosa Sherafat-Kazemzadeh, MD CBER/OTP/OCE/DCEGM/GMB2
Acting Super Office Director	Megha Kaushal, MD CBER/OTP
Applicant	Fondazione Telethon ETS / FTE
Established Name	Etuvetidigene autotemcel
(Proposed) Trade Name	WASKYRA
Pharmacologic Class	Hematopoietic stem cell-based gene therapy
Formulation(s), including Adjuvants, etc.	Autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) transduced <i>ex vivo</i> with a replication incompetent self-inactivating (SIN) human immunodeficiency virus-1 (HIV-1)-based lentiviral vector (LVV), modified to carry the WAS gene sequence under the control of the human WAS promoter
Dosage Form(s) and Route(s) of Administration	Transduced CD34+ cells are washed and cryopreserved in a suspension for intravenous infusion, containing 2–11.4 x 10 ⁶ cells /mL (1.9 –11.4 x 10 ⁶ CD34+ cells/mL)
Dosing Regimen	Minimum recommended dose is 7.0×10 ⁶ CD34 ⁺ cells/kg via intravenous infusion
Indication(s) and Intended Population(s)	Treatment of pediatric patients aged six 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
Orphan Designated (Yes/No)	Yes

TABLE OF CONTENTS

GLOSSARY	1
1. EXECUTIVE SUMMARY	3
1.1 Demographic Information: Subgroup Demographics and Analysis Summary	7
1.2 Patient Experience Data	8
2. CLINICAL AND REGULATORY BACKGROUND	10
2.1 Disease or Health-Related Condition(s) Studied	10
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)	12
2.4 Previous Human Experience with the Product (Including Foreign Experience)	13
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission	13
3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES	14
3.1 Submission Quality and Completeness	14
3.2 Compliance With Good Clinical Practices And Submission Integrity	14
3.3 Financial Disclosures	15
4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	15
4.1 Chemistry, Manufacturing, and Controls	15
4.2 Assay Validation	16
4.3 Nonclinical Pharmacology/Toxicology	16
4.4 Clinical Pharmacology	16
4.4.1 Mechanism of Action	16
4.4.2 Human Pharmacodynamics	16
4.4.3 Human Pharmacokinetics	16
4.4.4 Immunogenicity	16
4.4.5 Dose Evaluation	17
4.5 Statistical	19
4.6 Pharmacovigilance	19
5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW	20
5.1 Review Strategy	20
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review	20
5.3 Table of Studies/Clinical Trials	21
5.5 Literature Reviewed (if applicable)	24
6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS	26
6.1 Trial #1: A Phase 1/2 Clinical Trial of Hematopoietic Stem Cell Gene Therapy for the Wiskott-Aldrich Syndrome (TIGET-WAS/201228)	26
6.1.1 Objectives (Primary, Secondary, etc)	26
6.1.2 Design Overview	26
6.1.3 Population	27
6.1.4 Study Treatments	27
6.1.5 Directions for Use	28
6.1.6 Sites and Centers	28
6.1.7 Surveillance/Monitoring	28
6.1.8 Endpoints and Criteria for Study Success	30
6.1.9 Statistical Considerations & Statistical Analysis Plan	33
6.2 Trial # 2: A Single-Arm, Open-Label Clinical Study of Hematopoietic Stem Cell Gene Therapy with Cryopreserved Autologous CD34+ Cells Transduced with Lentiviral	

Vector encoding WAS Complementary DNA in Patients with Wiskott Aldrich Syndrome	33
6.2.1 Objectives (Primary, Secondary, etc).....	33
6.2.2 Design Overview	34
6.2.3 Population.....	34
6.2.4 Study Treatments or Agents Mandated by the Protocol	34
6.2.5 Directions for Use	35
6.2.6 Sites and Centers.....	35
6.2.7 Surveillance/Monitoring	35
6.2.8 Endpoints and Criteria for Study Success.....	35
6.2.9 Statistical Considerations & Statistical Analysis Plan	36
6.3 Expanded Access Program	37
7. INTEGRATED OVERVIEW OF EFFICACY	37
7.1 Indication #1	37
7.1.1 Methods of Integration.....	37
7.1.2 Demographics and Baseline Characteristics	37
7.1.3 Patient Disposition.....	38
7.1.4 Analysis of Primary Endpoint(s)	39
7.1.5 Analysis of Secondary Endpoint(s)	43
7.1.6 Other Endpoints.....	50
7.1.7 Subpopulations.....	51
7.1.8 Persistence of Efficacy	53
7.1.9 Product-Product Interactions.....	53
7.1.10 Additional Efficacy Issues/Analyses	53
7.1.11 Efficacy Conclusions	53
8. INTEGRATED OVERVIEW OF SAFETY	54
8.1 Safety Assessment Methods	54
8.2 Safety Database	54
8.2.1 Studies/Clinical Trials Used to Evaluate Safety	54
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations	54
8.2.3 Categorization of Adverse Events	56
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials	56
8.4 Safety Results	57
8.4.1 Deaths	57
8.4.2 Nonfatal Serious Adverse Events.....	57
8.4.3 Study Dropouts/Discontinuations	58
8.4.4 Common Adverse Events.....	58
8.4.5 Clinical Test Results	59
8.4.6 Systemic Adverse Events.....	61
8.4.7 Local Reactogenicity	61
8.4.8 Adverse Events of Special Interest	62
8.5 Additional Safety Evaluations	65
8.5.1 Dose Dependency for Adverse Events	65
8.5.2 Time Dependency for Adverse Events.....	65
8.5.3 Product-Demographic Interactions.....	65
8.5.4 Product-Product Interactions	65
8.5.5 Human Carcinogenicity	66
8.5.7 Immunogenicity (Safety).....	66
8.5.8 Person-to-Person Transmission, Shedding.....	66
8.5.9 One-Hundred Twenty-Day Safety Update.....	66

8.6 Safety Conclusions	67
9. ADDITIONAL CLINICAL ISSUES	68
9.1 Special Populations	68
9.1.1 Human Reproduction and Pregnancy Data.....	68
9.1.2 Use During Lactation	68
9.1.3 Pediatric Use and PREA Considerations	68
9.1.4 Immunocompromised Patients	68
9.1.5 Geriatric Use.....	68
9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered	68
10. CONCLUSIONS	68
11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS	69
11.1 Risk-Benefit Considerations	69
11.2 Risk-Benefit Summary and Assessment	73
11.3 Discussion of Regulatory Options	74
11.4 Recommendations on Regulatory Actions	74
11.5 Labeling Review and Recommendations	74
11.6 Recommendations on Postmarketing Actions	77

TABLE OF TABLES

Table 1: Demographic Characteristics at Screening/Baseline or on Date of Gene Therapy .	7
Table 2: Patient Experience Data Submitted in the Application	9
Table 3: Wiskott-Aldrich Syndrome Clinical Scoring System	12
Table 4: U.S. Regulatory Milestones	13
Table 5: Clinical Studies and Expanded Access Program in the WASKYRA Clinical Development Program (at the Time of Data Cut-Off)	21
Table 6: Baseline Characteristics of Efficacy Population	38
Table 7: Patient Disposition	38
Table 8: Statistics of Cells Expressing WASP, Efficacy Population	46
Table 9: Statistics of T-Cell Function, Efficacy Population	48
Table 10: Study Population Data, Safety Population	55
Table 11: Exposure to Rituximab and Conditioning Regimen	56
Table 12: Exposure to WASKYRA	56
Table 13: Nonfatal Serious Adverse Events Affecting ≥Two Patients	57
Table 14: Adverse Events Affecting ≥30% of Patients	58
Table 15: Patients with Immune-Mediated Adverse Events by System Organ Class, Preferred Term, and Treatment Phase, Safety Population	63
Table 16: Number of Patients with Adverse Events by Treatment Phase, Safety Population	65
Table 17: Risk-Benefit Considerations	70
Table 18: Summary of Significant Labeling Changes	74

TABLE OF FIGURES

Figure 1: Treatment Dose Vs. T Cell Proliferation Responses at Year 1, Efficacy Population	17
Figure 2: Treatment Dose Vs. Engraftment at Year 1 and Year 2, Efficacy Population	18
Figure 3: Treatment Dose Vs. WASP Expression in Platelets and Lymphocytes at Year 1 and Year 2, Efficacy Population	19
Figure 4: Severe Infections Over Time in WASKYRA-Treated Patients	41
Figure 5: Moderate and Severe Bleeding Events Over Time	42
Figure 6: Median Values for VCN/Cell in Bone Marrow Cell Lineages, Efficacy Population	44

Figure 7: Median Values for VCN/Cell in Peripheral Blood Cell Lineages, Efficacy Population	45
Figure 8: Median Values of Peripheral Blood Cells Expressing WASP Assessed by Flow Cytometry Over Time, Efficacy Population.....	46
Figure 9: Median (95% Confidence Interval) Values of Mean Platelet Count and Platelet Volume Over Time, Efficacy Population	49
Figure 10: Individual Profiles of Physical Growth (Height and Weight) Over Time.....	60

GLOSSARY

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BIMO	BioResearch Monitoring
BLA	Biologics License Application
BM	bone marrow
CBER	Center for Biologics Evaluation and Research
CD3i	immobilized CD3
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate Use Program
DMSO	dimethyl sulfoxide
EAP	Expanded Access Program
ECG	electrocardiogram
eCRF	electronic Case Report Form
FACS	fluorescence-activated cell sorting
FDA	U.S. Food and Drug Administration
GT	gene therapy
HE	Hospital Exemption
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
HSPC	hematopoietic stem and progenitor cells
G-CSF	granulocyte-colony stimulating factor
GVHD	graft-versus-host disease
Ig	immunoglobulin
IgRT	immunoglobulin replacement therapy
IND	Investigational New Drug
LDH	lactate dehydrogenase
LVV	lentiviral vector
MedDRA	Medical Dictionary for Regulatory Activities
mPB	mobilized peripheral blood
MPV	mean platelet volume
OS	overall survival
PB	peripheral blood
PCR	polymerase chain reaction
PMR	postmarketing requirement
PT	Preferred Term
PYO	person-year of observation
RCL	replication-competent lentivirus
RIC	Reduced intensity conditioning
SAE	serious adverse event
SMQ	Standardized MedDRA Query
TCR	T-cell receptor
TPO	thrombopoietin
ULN	upper limit of normal

USPI	United States Prescribing Information
VCN	vector copy number
VOD	veno-occlusive liver disease
WAS	Wiskott-Aldrich syndrome
WASP	Wiskott-Aldrich syndrome protein

1. EXECUTIVE SUMMARY

On January 10, 2025, Fondazione Telethon ETS submitted an original BLA, STN BL 125846, for licensure of etuvetidigene autotemcel (also known as Telethon003; proprietary name WASKYRA). The Applicant proposed the indication for treatment of Wiskott-Aldrich Syndrome in patients aged 6 months and older who have a mutation in the WAS gene and for whom no suitable HLA-matched related HSCT donor is available.

Wiskott-Aldrich syndrome is a rare, X-linked, recessive genetic disease caused by mutations in the WAS gene. It is characterized by microthrombocytopenia, eczema, recurrent infections, and increased susceptibility to autoimmunity and lymphoreticular malignancies. The syndrome affects multiple cellular functions in hematopoietic cells, leading to reduced platelet count and function, impaired T-cell and natural killer cell function, and defective antibody production. WAS is life-threatening, with severely reduced life expectancy without intervention.

There are no FDA-approved therapies for WAS, but current treatments include symptomatic management and allogeneic hematopoietic stem cell transplantation (HSCT), with the latter being more effective when performed early in life with matched donors.

WASKYRA (etuvetidigene autotemcel) is a gene therapy (GT) product for WAS consisting of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) transduced *ex vivo* with a replication-deficient lentiviral vector (LVV) encoding the human WAS gene. Patients undergo hematopoietic stem cell mobilization and apheresis to obtain CD34+ cells for transduction. Following a reduced intensity conditioning with rituximab, busulfan, and fludarabine, the transduced cells are administered via intravenous infusion to reconstitute the hematopoietic system with cells containing the integrated WAS gene. This approach aims to restore functional WAS protein expression in affected cells, addressing the underlying cause of the disease.

The clinical program for WASKYRA included two open-label, single-arm studies (TIGET-WAS and OTL-103-4) and two Expanded Access Program (EAP; Studies 205030, Hospital Exemption [HE], and 206257, Compassionate Use Program [CUP]), providing substantive evidence of effectiveness and safety from pooled data of 27 pediatric and adult male patients with severe WAS. The clinical studies enrolled 28 patients, of whom 27 were treated and included in the efficacy analyses. Patients were classified as having severe WAS based on the presence of at least one of the following three criteria: (i) a Zhu clinical score ≥ 3.0 , (ii) a severe WAS mutation, or (iii) absent Wiskott-Aldrich syndrome protein (WASP) expression. The Zhu score, a five-point scale assessing disease severity, considers factors such as thrombocytopenia, eczema, immunodeficiency, infections, autoimmunity, and malignancies. Severe WAS mutations typically included nonsense mutations, deletions, and insertions resulting in absent WASP expression or truncated WASP. Absent WASP expression was defined as $<5\%$ of lymphocytes expressing WASP. In the study population, 25 out of 27 patients had a Zhu score ≥ 3.0 at baseline, indicating severe clinical disease. Additionally, 22 out of 27 patients were identified as having severe WAS mutations, while the severity was unknown for the remaining 5 patients.

The primary efficacy endpoints for the integrated analysis of WASKYRA in treating WAS were: (i) overall survival, (ii) the rate of severe infections from 6 to 18 months post-treatment compared to the 12 months before treatment, and (iii) the rate of moderate and severe bleeding events in the first 12 months post-treatment compared to the 12 months before treatment.

Severe Infections

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

There was an increase in the rate of severe infections in the first 6 months following WASKYRA infusion (3.15 infections per PYO). This was attributed to the patients' increased vulnerability during immune system reconstitution after conditioning. However, the infection rate significantly decreased after this initial period. The reduction in severe infection rates was consistent across different studies within the WASKYRA program, indicating comparable treatment effects between fresh and cryopreserved formulations of Telethon-003. This improvement in infection rates occurred despite the normalization of patients' social interactions and the discontinuation of immunoglobulin replacement therapy (IgRT) and sustained antimicrobial treatment in most patients.

Moderate and Severe Bleeding

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

The rate of moderate and severe bleeding events decreased from 2.00 (95% CI: 1.50-2.61) events per PYO in the 12 months before GT to 0.80 (95% CI: 0.49-1.22) events per PYO in the 12 months following WASKYRA infusion. This reduction was even more pronounced in the long-term follow-up, with the rate decreasing to 0.03 (95% CI: 0.003-0.099) events per PYO in the >4-year period post-treatment. When analyzed separately, both moderate and severe bleeding events showed significant reductions. The rate of severe bleeding events decreased from 0.89 events per PYO before treatment to 0.08 events per PYO in the 12 months post-treatment, while moderate bleeding events decreased from 1.11 to 0.72 events per PYO in the same period.

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

Safety

The safety evaluation of WASKYRA is based on comprehensive data from 27 patients with WAS treated across two clinical studies (TIGET-WAS and OTL-103-4) and the EAP. The median age at treatment was 2.56 years with a range from 0.98 to 35.1 years; patients were followed for a median duration of 5.67 years, with some patients followed for up to 13.26 years.

Mortality and Serious Adverse Events

One death occurred in the study population involving a 35-year-old patient who died approximately 4.5 months after WASKYRA treatment due to deterioration of a preexisting neurological condition. The treating physician considered this death unrelated to WASKYRA, though relatedness to the conditioning regimen could not be definitively excluded. A total of 67 serious adverse events (SAEs) were reported in 22 patients (81.5%), with the majority (52.2%) occurring within the first 6 months post-treatment during the period of immune reconstitution. The most common SAEs included device-related infections (11 [40.7%]), pyrexia (5 [18.5%]), and gastroenteritis (3 [11.1%]). Importantly, none of the SAEs were considered related to WASKYRA treatment itself.

Common Adverse Events

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

Adverse Events of Special Interest

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

Oncogenicity Assessment

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

The overall safety profile of WASKYRA is considered acceptable for the treatment of severe WAS. The majority of AEs were attributable to the underlying disease pathophysiology, the intensive conditioning regimen consisting of rituximab, busulfan, and fludarabine, or the

expected period of immune reconstitution following treatment. No AEs were directly attributed to WASKYRA treatment itself, and the observed safety profile aligns with expectations for a GT requiring myeloablative conditioning in an immunocompromised patient population.

Long-Term Monitoring and Risk Management

Recognizing the limitations of the relatively small safety database and the theoretical long-term risks associated with lentiviral GT, a comprehensive postmarketing requirement study has been established. This includes a 15-year observational study of 40 patients to monitor for long-term safety outcomes, with particular emphasis on the potential development of secondary malignancies. This extended surveillance will provide crucial data on the long-term safety profile of WASKYRA and help characterize any delayed adverse effects that may emerge over time.

Conclusion

The efficacy evaluation of WASKYRA demonstrates substantial clinical benefit for patients with severe WAS, with significant reductions in the primary disease manifestations that drive morbidity and mortality. The rate of severe infections decreased dramatically from 2.00 infections per PYO in the 12 months before treatment to 0.16 infections per person-year in the 6 to 18-month period post-treatment. Similarly, moderate and severe bleeding events were reduced from 2.00 events per person-year pre-treatment to 0.80 events per person-year in the first 12 months post-treatment, with further improvement to 0.03 events per person-year beyond 4 years. These clinical improvements were supported by sustained engraftment of genetically corrected cells in all patients, marked increases in WASP expression across multiple cell lineages, normalization of platelet counts with cessation of transfusion dependence, and restoration of T-cell function. The durability of these benefits, demonstrated over follow-up periods extending up to 13.26 years, indicates that WASKYRA provides long-term correction of the underlying genetic defect.

The safety profile of WASKYRA is acceptable given the life-threatening nature of severe WAS and the limited treatment alternatives for patients without suitable matched donors. While all 27 patients experienced AEs, these were primarily attributable to the underlying immunodeficiency, the required conditioning regimen, or the expected immune reconstitution period rather than the GT itself. The single death was related to a pre-existing neurological condition and was not considered treatment-related, though conditioning effects could not be excluded. Importantly, no evidence of insertional oncogenesis was observed during the study period, and most SAEs resolved without sequelae. The establishment of a 15-year postmarketing study will provide essential long-term safety data, particularly regarding potential delayed malignancies.

The review team recommends traditional approval for WASKYRA for the treatment of pediatric patients aged 6 months and older and adults with Wiskott-Aldrich Syndrome (WAS) who have a mutation in the WAS gene for whom hematopoietic stem cell transplantation (HSCT) is appropriate and no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Regulatory Flexibility

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

During WASKYRA's review, the FDA exercised regulatory flexibility across three critical areas: mechanism of action, clinical trial design, and rare disease considerations. The rare disease context encompassed both the limited patient population and the significant unmet medical need in patients lacking suitable HLA-matched donors for conventional HSCT. The agency accepted open-label, single-arm studies and incorporated real-world data from the Expanded Access Program (EAP), which provided substantive evidence of effectiveness. The gene therapy's direct targeting of the underlying genetic defect in WAS provides critical mechanistic support for the observed clinical benefits. This regulatory flexibility enabled access to a therapeutic option that demonstrated robust and sustained clinical improvements with an acceptable safety profile in patients with this life-threatening rare disease.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Twenty-seven patients were treated with WASKYRA in 2 single-arm clinical studies and the expanded access cohort. All patients were male and the majority (20 [74.1%] patients) were White. Age at the time of GT ranged from 1.0 to 35.1 years, with 11 patients <24 months, 11 patients ≥24 months to 11 years, and 5 patients >11 years. At the time of treatment, 33.3% of patients were ≥5 years old.

Table 1: Demographic Characteristics at Screening/Baseline or on Date of Gene Therapy

Demographic Characteristics	WASKYRA (N=27)
Age on date of gene therapy in years, median (range)	2.562 (0.98, 35.06)
Age group on date of gene therapy, n (%)	-
28 days to <24 months	11 (40.7)
≥24 months to 11 years	11 (40.7)
>11 years	5 (18.5)
Age group (5 year cut-off categories) on date of gene therapy, n (%)	-
<5 years	18 (66.7)
≥5 years	9 (33.3)
Age group (based on ICH categories) on date of gene therapy	-
28 days to <24 months	11 (40.7)
≥24 months to <12 years	12 (44.4)
12 years to <18 years	2 (7.4)
≥18 years	2 (7.4)
Sex, n (%) ^a	-
Male	27 (100)
Race, n (%) ^a	-
American Indian or Alaska Native	1 (3.7)
Asian	4 (14.8)
Black or African American	2 (7.4)
White	20 (74.1)
Ethnicity, n (%)	-
Not Hispanic or Latino	24 (88.9)
Hispanic or Latino	3 (11.1)
Height in cm, median (min, max) ^b	89.40 (66.0, 172.0)
Weight in kg, median (min, max) ^b	12.770 (7.59, 70.00)
Body mass index in kg/m ² , median (min, max) ^b	16.875 (13.76, 24.34)
Body surface area in m ² , median (min, max) ^b	0.568 (0.38, 1.82)
Country of Residence, n (%)	-
Albania	1 (3.7)
Bolivia	1 (3.7)
Canada	1 (3.7)
Germany	1 (3.7)

Demographic Characteristics	WASKYRA (N=27)
Italy	10 (37.0)
Japan	1 (3.7)
Lebanon	1 (3.7)
Mauritius	1 (3.7)
Romania	1 (3.7)
Russian Federation	3 (11.1)
Spain	1 (3.7)
Trinidad and Tobago	1 (3.7)
Turkey	1 (3.7)
United States	2 (7.4)
Venezuela	1 (3.7)
Site of enrollment	-
SR-TIGET ^c	26 (96.3)
CHOA ^d	1 (3.7)
Time between diagnosis and informed consent (years)	-
Median (min, max)	0.732 (0.02,33.18)

Source: Adapted from Integrated Summary of Efficacy***, page 44

^a Sex and race are summarized based on data collected at screening.

^b Height and weight including the calculated BMI and body surface area are based on the last measurement collected prior to treatment phase.

^c San Raffaele Telethon Institute for Gene Therapy, San Raffaele Hospital, Milan, Italy.

^d Children's Healthcare of Atlanta/ Emory University School of Medicine, USA.

Abbreviations: BM, bone marrow; CHOA, Children's Healthcare of Atlanta; Cryo, mPB Cryopreserved; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; Max, maximum; Min, minimum; mPB, mobilized peripheral blood; n (%), number of patients with the specified characteristic; N, number of patients in the specified group, or the total sample; SD, standard deviation; SR-TIGET, San Raffaele Telethon Institute for Gene Therapy

Reviewer Comment: *The patients treated with WASKYRA in the clinical studies are considered generally representative of patients with severe WAS in the United States. The study enrolled primarily patients who were White/Caucasian, not Hispanic or Latino, and from countries outside the United States. This is not unexpected given that the highest prevalence of WAS has been observed in North American and European populations. Additionally, the clinical studies were conducted at a single site in Italy enrolling primarily European patients. Based on the pathophysiology of WAS, there are no known differences in clinical course based on race, ethnicity, and country of origin.*

1.2 Patient Experience Data

The patient perspective was considered and incorporated throughout this review based on information from the following sources:

- Externally-Led Patient Focused Drug Development on WAS and X-linked thrombocytopenia held on February 3, 2023 (Wiskott-Aldrich Foundation 2023)
- Wiskott-Aldrich Syndrome Worldwide Patient Outcomes Survey Report (release date of report: October 26, 2021). Please refer to Dr. Gu's Real World Evidence review memo for detailed discussion of this report. Briefly, the Albert survey reports findings of 577 patients with WAS from major medical centers treating patients with primary immunodeficiency diseases in the world from 1990 to 2014.
 - Nearly half (48%) of the patients were from Europe; 20% were from the United States, and 32% were from the rest of the world. Most patients (79%) were diagnosed before 5 years old.

- b. For treatment, 46% patients received only supportive treatments, and patients treated with HSCT, splenectomy, and GT accounted for 46%, 14%, and 2.4%, respectively.
- c. Overall, 36% had mild WAS (Zhu score 1-2), and 64% had severe WAS (Zhu 3-5).
- d. The OS at 15 years was 78%, and 60% of deaths (n=113) occurred before age of 5 years.
- e. For severe clinical events including severe infections, serious bleeding episodes, autoimmunity and malignancy, the event-free survival at 15 years was 33%. The most common serious clinical event was infection, experienced by 205 (37.3%) patients. The second most common serious event was bleeding, experienced by 124 (22.5%) patients. Ninety-five (17.3%) patients experienced at least one autoimmunity event before their first procedure or before their last follow-up. Fourteen (2.5%) patients experienced a malignancy event before their first procedure or before their last follow-up.

Table 2: Patient Experience Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input checked="" type="checkbox"/>	Observational survey studies	1.2 Patient Experience Data
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input checked="" type="checkbox"/>	Patient-focused drug development meeting	Reviewed ¹
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

¹ [Externally-Led Patient Focused Drug Development on Wiskott-Aldrich Syndrome \(WAS\) and X-Linked Thrombocytopenia \(XLT\) Voice of the Patient Report, Meeting Date: February 3, 2023](#)

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Introduction and Genetics

Wiskott-Aldrich syndrome is a rare, X-linked, primary immunodeficiency disorder first described by Wiskott in 1937 and later characterized by Aldrich in 1954. This severe combined immunodeficiency and platelet disorder is caused by mutations in the *WAS* gene located on the X chromosome at position Xp11.22-23. The *WAS* gene encodes the WASP, a 502-amino acid cytoskeletal regulator that is exclusively expressed in hematopoietic cells, including platelets, lymphocytes, neutrophils, and monocytes.

The Wiskott-Aldrich syndrome protein plays a crucial role in actin polymerization and cytoskeletal reorganization, serving as a key mediator in multiple cellular processes essential for immune function. The protein is critical for cell adhesion, migration, phagocytosis, immune synapse formation, and receptor-mediated cellular activation processes. It facilitates the assembly of the immunological synapse between T-cells and antigen-presenting cells, making it fundamental for adaptive immune responses. Additionally, WASP is essential for proper platelet function and morphology, explaining the characteristic thrombocytopenia observed in affected patients.

Over 400 unique mutations have been identified in the *WAS* gene, demonstrating remarkable genetic heterogeneity with complex genotype-phenotype correlations. Mutations are classified into two main categories based on their functional consequences. Class I variants consist primarily of missense mutations in exons 1 and 2 that result in reduced but detectable WASP expression, traditionally associated with milder phenotypes. Class II variants include nonsense mutations, splice site mutations, deletions, and insertions that typically result in absent or severely truncated WASP protein, historically linked to more severe disease manifestations.

However, recent comprehensive studies have challenged this traditional classification, demonstrating that patients with any *WAS* mutation type can develop severe complications over time. The progressive nature of the disease means that even patients initially presenting with mild phenotypes may evolve to severe manifestations, emphasizing the importance of early recognition and intervention regardless of initial mutation classification.

Epidemiology

Wiskott-Aldrich syndrome is an ultra-rare disorder with an estimated incidence of 1 in 100,000 to 1 in 1,000,000 live male births. Due to its X-linked inheritance pattern, the syndrome predominantly affects males, though rare cases of affected females have been reported due to skewed X-inactivation patterns or chromosomal abnormalities. The disease occurs across all ethnic populations worldwide, though access to optimal treatment varies significantly based on geographic location and healthcare infrastructure. Recent international collaborative studies have documented over 500 patients globally, providing valuable insights into disease prevalence and natural history. The syndrome shows no particular ethnic predilection, though the availability of suitable hematopoietic stem cell donors for transplantation varies considerably based on ethnicity and geographic ancestry. Non-Caucasian patients face particular challenges in finding matched unrelated donors due to the limited diversity in donor registries, with only approximately two-thirds of patients able to identify a 10/10 matched unrelated donor.

Clinical Course

WAS presents with a characteristic triad of clinical features: microthrombocytopenia with bleeding tendency, eczema, and recurrent infections. However, the clinical spectrum is broad and can include additional severe manifestations such as autoimmunity, autoinflammation, and increased susceptibility to malignancies.

Thrombocytopenia and Bleeding

Universal among patients with WAS, thrombocytopenia is characterized not only by reduced platelet counts but also by characteristically small platelet size (microthrombocytopenia) and functional defects. Bleeding manifestations occur in over 80% of patients before diagnosis, with approximately 30% experiencing severe bleeding episodes including hematemesis, melena, and potentially life-threatening intracranial hemorrhage. The bleeding tendency results from both quantitative and qualitative platelet abnormalities due to disrupted cytoskeletal organization affecting platelet function and morphology.

Immunodeficiency and Infections

The immune dysfunction in WAS is multifaceted, affecting both cellular and humoral immunity. Patients demonstrate impaired T-cell proliferation and function, defective antibody responses particularly to polysaccharide antigens, reduced natural killer cell cytotoxicity, and abnormal dendritic cell migration and function. This broad immunodeficiency results in increased susceptibility to bacterial, viral, fungal, and opportunistic infections. Common infectious complications include recurrent upper respiratory tract infections, pneumonia, sepsis, meningitis, and opportunistic infections such as *Pneumocystis jirovecii* pneumonia. Viral infections, particularly cytomegalovirus and Epstein-Barr virus, can be severe and life-threatening.

Eczema

Affecting approximately 80% of patients, eczema in WAS can range from mild, transient skin changes to severe, therapy-resistant atopic dermatitis. The eczema often has an atypical distribution and severity compared to classic atopic dermatitis and may be complicated by secondary bacterial or viral skin infections due to the underlying immunodeficiency and frequent skin barrier disruption.

Autoimmunity and Malignancy

As patients age, they face increasing risks of autoimmune manifestations including autoimmune hemolytic anemia, immune thrombocytopenic purpura, inflammatory bowel disease, vasculitis, and arthritis. The syndrome also carries a significantly elevated risk of developing lymphoreticular malignancies, particularly non-Hodgkin lymphomas and leukemias, with risk increasing substantially with age.

It is noteworthy that WAS presents as a continuum of dysfunction from mild to severe, reflecting various degrees of WASP deficiency or loss of function. Disease severity is assessed using the Zhu scoring system, which grades patients from 0.5 to 5 based on the presence and severity of thrombocytopenia, eczema, immunodeficiency, with additional designations for autoimmunity (5A) and malignancy (5M). This scoring system helps predict prognosis and guide treatment

decisions, though the disease typically progresses to higher scores over time without definitive intervention.

Table 3: Wiskott-Aldrich Syndrome Clinical Scoring System

Clinical Scores	XLT 0.5	XLT 1	XLT 2	WAS 3	WAS 4	WAS 5A	WAS 5M
Thrombocytopenia	+/-	+	+	+	+	+	+
Eczema	-	-	+/-	+	++	++/-	++/-
Immunodeficiency	-	-	+/-	+	++	++/-	++/-
Autoimmunity	-	-	-	-	-	+	-
Malignancy	-	-	-	-	-	-	+

Source: adapted from Zhu et al. 1997

The score is based on Zhu and colleagues (Zhu et al. 1997), with subsequent refinements (Bosticardo et al. 2009).

Abbreviations: WAS, Wiskott-Aldrich Syndrome; XLT, X-linked thrombocytopenia

The prognosis of WAS without definitive treatment is poor, with a median survival of approximately 14.5 years. The primary causes of death include severe infections (44% of cases), hemorrhage (23%), and malignancies (26%). The disease follows a progressive course, with patients experiencing increasing rates of disease-associated complications over time. Without curative intervention, the event-free survival for any serious clinical event is only 33% at 15 years of age, with the median time to first serious clinical event being 5 years.

Several factors influence prognosis, including age at diagnosis, mutation type, baseline disease severity, and access to appropriate medical care. Patients with Class I mutations generally demonstrate better long-term survival compared to those with Class II mutations, though both groups remain at risk for severe complications. The development of autoimmunity or malignancy significantly worsens prognosis, as reflected in the Zhu scoring system.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Current treatment options consist of conventional symptomatic and preventive management and allogeneic HSCT.

Supportive Care

Comprehensive supportive management forms the foundation of WAS care and includes multiple therapeutic interventions. Platelet transfusions are used for severe bleeding episodes or prophylaxis before surgical procedures, though repeated transfusions carry risks of alloimmunization that can complicate future treatments. Thrombopoietin receptor agonists, including romiplostim and eltrombopag, have shown efficacy in increasing platelet counts and are increasingly used off-label as bridging therapy or in patients unsuitable for definitive treatment.

Infection prevention strategies include IgRT to maintain adequate immunoglobulin (Ig)G levels above 5 g/L, prophylactic antimicrobials (particularly trimethoprim-sulfamethoxazole for Pneumocystis prophylaxis), and aggressive treatment of infections when they occur. Patients often require prolonged courses of antimicrobials and may need hospitalization for severe infections. Eczema management follows standard dermatological approaches with emollients, topical corticosteroids, and calcineurin inhibitors, though severe cases may require systemic immunosuppression.

Splenectomy

Historically performed to improve platelet counts, splenectomy can be effective in raising platelet numbers but carries significant long-term risks. These include increased susceptibility to encapsulated bacterial infections requiring lifelong antibiotic prophylaxis, and potential complications if subsequent HSCT becomes necessary. Modern practice has largely moved away from routine splenectomy in favor of medical management and definitive treatments.

Hematopoietic Stem Cell Transplantation

Currently considered the gold standard curative treatment for WAS, HSCT can restore normal immune function and correct the platelet defect when successful. Outcomes have improved dramatically over recent decades, with contemporary studies reporting 5-year OS rates approaching 90%. However, success rates vary considerably based on several critical factors:

Donor type significantly impacts outcomes, with matched sibling donors providing optimal results (>90% survival) but available to only approximately 30% of patients. Matched unrelated donors achieve survival rates of 75% to 85%, while alternative donors, including haploidentical relatives and cord blood, have historically shown lower success rates, though recent advances in transplant techniques have substantially improved outcomes with these donor sources.

Age at transplantation represents a crucial prognostic factor, with patients transplanted before age 5 years demonstrating significantly superior outcomes (94% survival) compared to those transplanted at age 5 or older (66% survival).

Disease severity at transplantation also affects outcomes, with patients having higher Zhu scores, particularly those with established autoimmunity or malignancy, experiencing worse transplant outcomes. This relationship emphasizes the importance of early intervention before the development of advanced disease complications.

Hematopoietic stem cell transplantation carries significant risks, including graft-versus-host disease (GVHD, occurring in approximately 27% of patients for Grade 2 to 4 acute GVHD and 14% for chronic GVHD), graft failure requiring rescue procedures (approximately 11% of patients), conditioning-related toxicity, and various long-term complications. The intensive immunosuppression required to prevent GVHD also increases infection risk in an already immunocompromised population.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

All except one patient received WASKYRA treatment in Italy. See [Section 6](#) and [Section 7](#) for detailed discussion.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 4 summarizes the main interactions between FDA and applicant from pre-IND planning stage in 2010 to BLA submission in 2025.

Table 4: U.S. Regulatory Milestones

Date	Milestone	Details
2010	Orphan Drug Designation	Initial orphan drug designation granted

Date	Milestone	Details
2017	Pre-IND Meetings	Pre-IND meetings and follow-up regarding clinical development program (CRMTS 10678)
2018	Rare Pediatric Disease Designation	Rare pediatric disease designation granted
2019	IND submission	IND safe to proceed
2019	RMAT Designation	Regenerative Medicine Advanced Therapy designation granted
March 2020	RMAT Eligibility Meeting	Meeting to evaluate RMAT designation eligibility and discuss cryopreserved formulation
February 2021	Development Meeting	Discussion of Study OTL-103-4 results and protocol changes
November 2024	Pre-BLA meeting	Engagement regarding future BLA submission requirements
December 2024	Rolling submission of BLA	Rolling BLA submission initiation (Modules 4, 5, and related Module 2 summaries
January 2025	Rolling submission of BLA	Module 1, 3 and related Module 2 summaries submitted.

Source: FDA

Abbreviations: BLA, Biologics License Application; IND, Investigational New Drug; RMAT, Regenerative Medicine Advanced Therapy; U.S., United States

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The two interventional studies (Studies TIGET-WAS and OTL-103-4), as well as the expanded access studies (Studies 205030, Hospital Exemption [HE], and 206257, Compassionate Use Program [CUP]), were performed in compliance with good clinical practice.

Bioresearch Monitoring (BIMO) inspections were conducted at two clinical sites. The inspection assignment included specific questions related to the study protocols, and information submitted in the BLA was compared to source documents at the clinical site.

Study TIGET-WAS (201228) was conducted at one site in Italy, which enrolled a total of 8 subjects. Study OTL-103-4 was conducted at two sites across the United States and Italy, enrolling a total of 10 subjects. The one CI site inspected in support of this BLA covered 100% and 90% of the total study population enrolled in TIGET-WAS and OTL-103-4, respectively.

INSPECTION SUMMARY AND OUTCOME

The inspections verified the data reported in the BLA, including but not limited to subject eligibility, study drug administration, protocol deviations, and adverse events for the reviewed subjects enrolled at the inspected clinical site. The inspections did not reveal any issues that impact the data submitted in this application (FDA BIMO Letters).

3.3 Financial Disclosures

Covered clinical study (name and/or number): TIGET-WAS, OTL-103-4, HE/CUP
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <u>16</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>16</u>
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>16</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p> <p>Is an attachment provided with details of the disclosable financial interests/arrangements? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant)</p> <p>Is a description of the steps taken to minimize potential bias provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant)</p>
<p>Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>N/A</u></p> <p>Is an attachment provided with the reason? <input type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant)</p>

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

WASKYRA consists of a cell population originating from HSPCs enriched for CD34+ cells and transduced with an LVV encoding the complementary DNA for WAS protein (WASP). WASP is a cytoskeletal regulator that promotes actin polymerization in cells of lymphoid and myeloid lineages. WASKYRA is manufactured from autologous mobilized peripheral blood (mPB) material. Following the completion of manufacturing, drug product is formulated at 2 to (b) (4) $\times 10^6$

cells/mL and is cryopreserved in 0.9% NaCl, 5% dimethyl sulfoxide (DMSO), and 7% human serum albumin prior to storage at <-130°C. The formulated cell suspension is filled into one to eight storage bags, each containing a volume of 10 to 20 mL. Please refer to Dr. DeMaster's CMC review memo for details.

4.2 Assay Validation

Please refer to the CMC review memo.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the pharmacology/toxicology review memo.

4.4 Clinical Pharmacology

The clinical pharmacology information in the current BLA includes data from Study TIGET-WAS and Study OTL-103-4. Refer to [Section 6](#) for the details of these studies.

4.4.1 Mechanism of Action

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

4.4.2 Human Pharmacodynamics

The engraftment of genetically corrected cells and WASP gene expression were evaluated with following pharmacodynamic biomarkers as secondary efficacy endpoints: genetically corrected cell engraftment (as evaluated by vector copy number [VCN]/cell, equivalent to percentage of gene-marked cells assuming a VCN of 1), WASP expression (in all peripheral blood [PB] cell types), T-cell function (represented by counts per minute and stimulation index), and platelet count. Based on data, adequate durable multi-lineage engraftment of gene-modified cells was observed in all patients, stable WASP expression in PB cells was observed, and T cell function was improved after WASKYRA administration. Refer to [Section 7.1.5](#) for details.

4.4.3 Human Pharmacokinetics

WASKYRA is a GT medicinal product consisting of autologous cells that have been genetically modified ex vivo. Results of replication-competent lentivirus testing were negative in all participants.

The nature of WASKYRA is such that conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

4.4.4 Immunogenicity

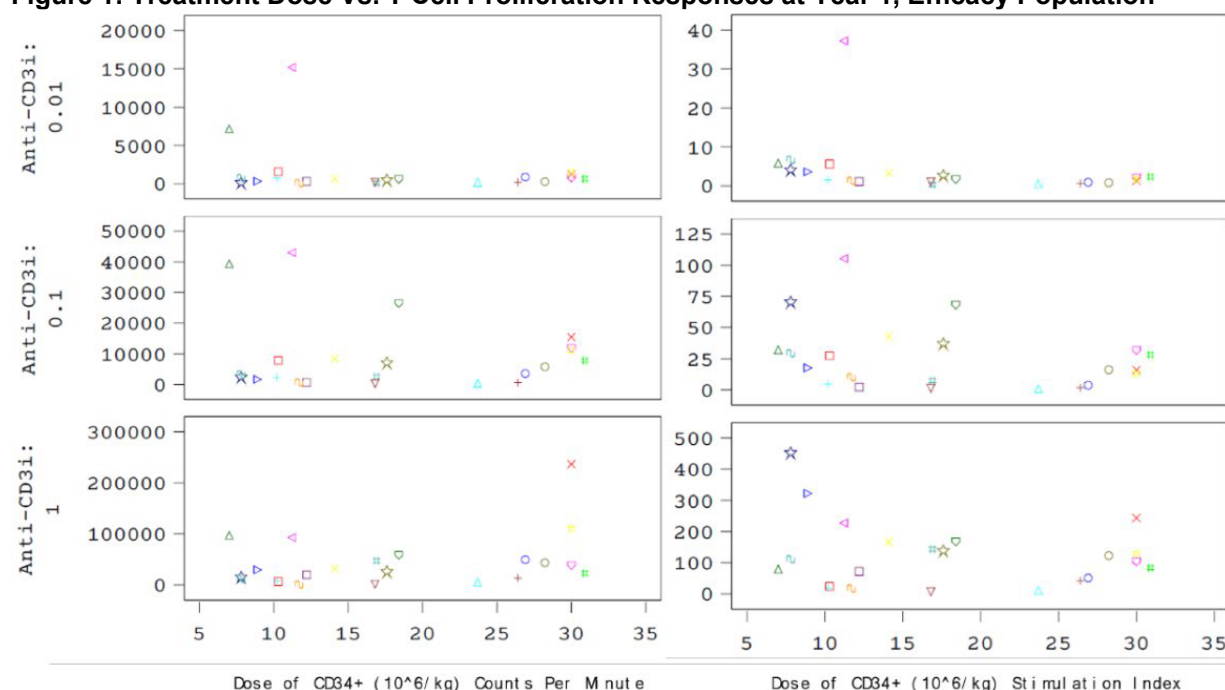
Refer to [Section 8.5.7](#) for immunogenicity information.

4.4.5 Dose Evaluation

A range of clinically relevant doses were studied in clinical studies of WASKYRA based on the number of HSPCs harvested for transduction for each patient: $7.0 - 30.9 \times 10^6/\text{kg}$ CD34+ cells (median dose: $16.9 \times 10^6/\text{kg}$). Based on the results of gene-corrected cell engraftment, T-cell function, and WASP expression, as shown in [Figure 1](#), [Figure 2](#), and [Figure 3](#) below, there is no evidence of correlation between WASKYRA cell dose and these responses.

Based on the clinical efficacy and safety results (refer to the safety assessment conclusion in [Section 8.6](#)), the Applicant proposed dosing regimen (a single dose of IV infusion with the minimum dose of 7×10^6 CD34+ cells/kg is acceptable.

Figure 1: Treatment Dose Vs. T Cell Proliferation Responses at Year 1, Efficacy Population



(b) (6)

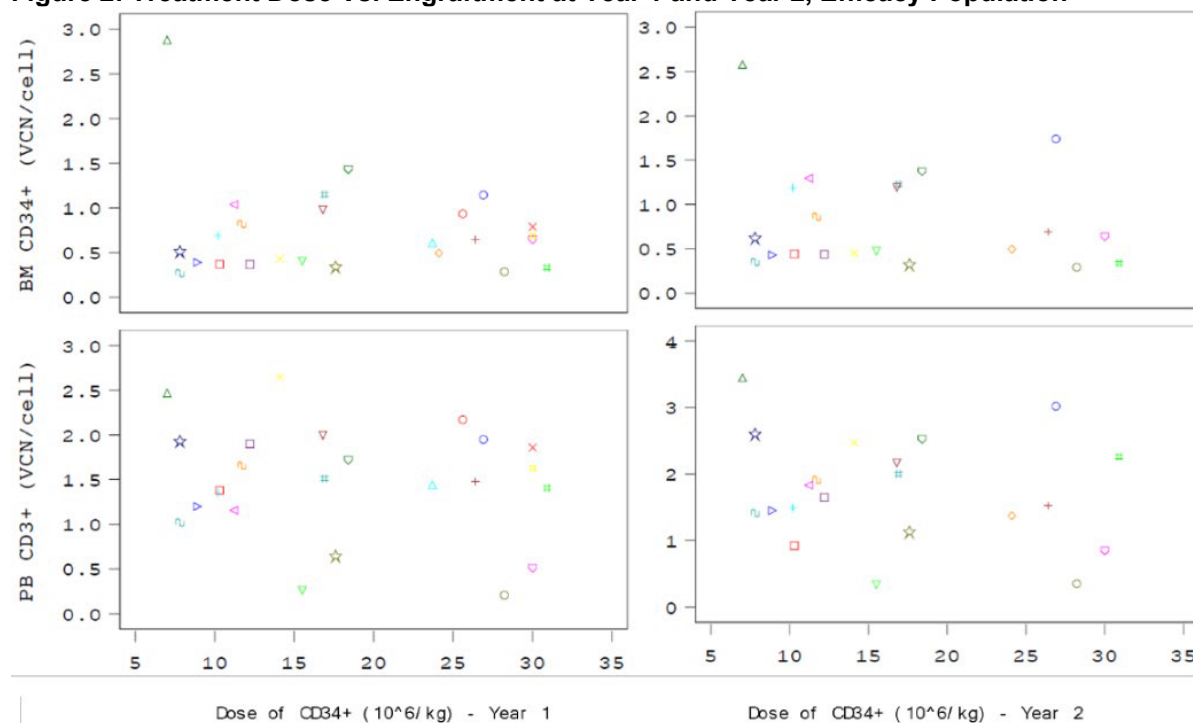
Source: Summary of Clinical Efficacy submitted by the Applicant

Note: Lymphocyte proliferation was assessed using different units (%) at the Children's Healthcare of Atlanta site to the SR-TIGET site. Therefore, lymphocyte proliferation data for the patient at the CHOA site is not summarized in this output.

Note: Patient (b) (6) received two separate doses of CD34+. The sum of the two doses is displayed in this plot.

Abbreviations: CD, cluster of differentiation; CD3i, immobilized CD3; CHOA, Children's Healthcare of Atlanta

Figure 2: Treatment Dose Vs. Engraftment at Year 1 and Year 2, Efficacy Population



(b) (6)

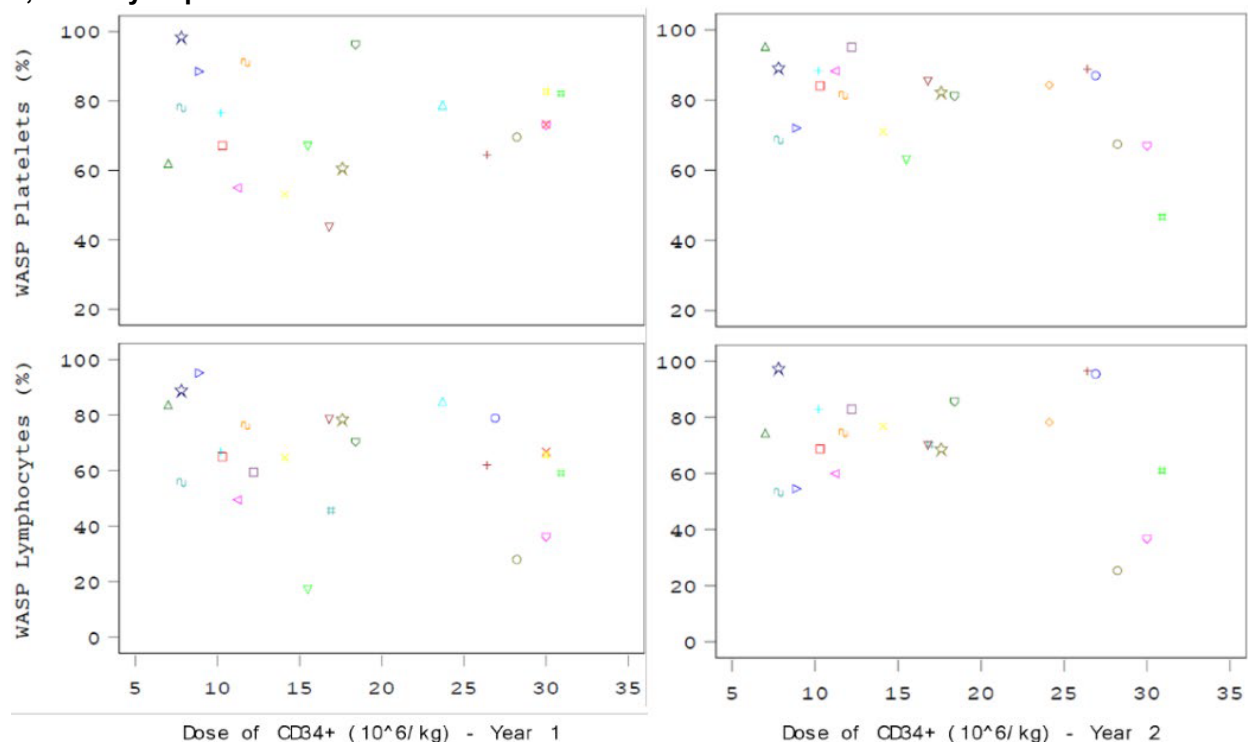
Source: Summary of Clinical Efficacy submitted by the Applicant

Note: Patient (b) (6) received two separate doses of CD34+. The sum of the two doses is displayed in this plot. In legend, abbreviated patient IDs are used. "TWXX" = TIGET-WAS patient, "HEXX" = HE patient, "CUPXX" = CUP patient, "OTLXX" = OTL-103-4 patient, (b) (6) = OTL-103-4 CHO site patient (b) (6).

Note: Visits are only presented if there are at least 2 patients with available data

Abbreviations: BM, bone marrow; CD, cluster of differentiation; CHO, Children's Healthcare of Atlanta; PB, peripheral blood; VCN, vector copy number

Figure 3: Treatment Dose Vs. WASP Expression in Platelets and Lymphocytes at Year 1 and Year 2, Efficacy Population



(b) (6)

Source: Summary of Clinical Efficacy submitted by the Applicant

Note: Patient (b) (6) received two separate doses of CD34+. The sum of the two doses is displayed in this plot. In legend, abbreviated patient IDs are used. "TWXX" = TIGET-WAS patient, "HEXX" = HE patient, "CUPXX" = CUP patient, "OTLXX" = OTL-103-4 patient, "(b) (6)" = OTL-103-4 CHO site patient (b) (6).

Note: Visits are only presented if there are at least 2 patients with available data.

Note: Patients enrolled at the CHO site do not have WASP expression assessed in platelets.

Abbreviations: CD, cluster of differentiation; CHO, Children's Healthcare of Atlanta; WASP, Wiskott-Aldrich syndrome protein

4.5 Statistical

Please refer to the statistical review memo.

4.6 Pharmacovigilance

We do not believe that Risk Evaluation and Mitigation Strategies are necessary or recommended based on the identified risks during the clinical studies, potential risks based on the product, and the limited target population. We believe that these risks can be adequately conveyed through labeling, including instructions for patient counseling.

The clinical review team agrees with the Division of Pharmacovigilance's recommendation for a postmarketing requirement (PMR) study under Food and Drug Administration Amendments Act of 2007 Title IX. The PMR will require the Applicant to conduct a postmarketing, prospective observational study to assess and characterize the risk of secondary malignancies and long-term safety. During clinical development, there were a limited number of patients treated with WASKYRA, and based on the size of the safety database, additional information is needed on long-term safety. Specifically, there was one malignancy reported as possibly related to the

conditioning regimen. In addition, this class of products has been associated with insertional oncogenesis. During the clinical study, there was a fatal SAE due to neurological decompensation that was determined not related to WASKYRA. The PMR study will provide a more comprehensive assessment of long-term risks and a better understanding of monitoring and potential risk mitigation. For additional discussion of the safety findings and analysis, please refer to [Section 8](#). Please refer to the Pharmacovigilance review for additional details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This BLA submission contained clinical data from two open-label, single-arm studies, TIGET-WAS and OTL-103-4, and an EAP in Italy. The TIGET-WAS study was conducted at a single site in Italy and completed at the time of data cut-off for integrated analyses of safety and efficacy on December 4, 2023. The study enrolled eight patients with a follow-up duration ranging from 8.0 to 13.3 years. Patients in the TIGET-WAS study received WASKYRA sourced from bone marrow (BM) or mPB in fresh formulation. The OTL-103-4 study was still ongoing at data cut-off with 8 of the 10 patients enrolled in the study having completed 2 years of follow-up. The OTL-103-4 study had two sites, one in Italy and one in the United States, although the U.S. site enrolled only one patient. Patients in the OTL-103-4 study received the commercial cryopreserved formulation of WASKYRA sourced from mPB. Patients in the EAP received fresh formulation of WASKYRA sourced from mPB. Neither of the two clinical studies was designed to be a registration study. Despite the difference in drug product formulations, the two clinical studies enrolled comparable patient populations, followed similar conditioning and treatment regimens, and showed similar findings in safety and efficacy. The TIGET-WAS study provided long-term safety and efficacy information, whereas the OTL-103-4 study confirmed safety and efficacy of the commercial drug product formulation. Both the clinical studies were considered pivotal for BLA review. Clinical experience from the EAP (HE/CUP) provided further confirmed safety and efficacy findings in the two clinical studies.

Given the small sample size and the rarity of the disease, analyses of safety and efficacy were pooled from Study TIGET-WAS, Study OTL-103-4, and the EAP datasets and are discussed in [Section 7](#). Individual clinical studies and key findings are described in [Section 6](#).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Source documents for this review include documents filed under the original application for BLA 125846 and documents under IND#18919, which include meeting minutes and correspondences between FDA and the Applicant.

5.3 Table of Studies/Clinical Trials

Table 5 below provides an overview of the clinical studies. Additional information on the clinical studies is presented in [Section 6](#).

Table 5: Clinical Studies and Expanded Access Program in the WASKYRA Clinical Development Program (at the Time of Data Cut-Off)

Study Identifier	Objective(s)	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients Treated	Study Status
TIGET-WAS (also known as 201228) NCT01515462 EudraCT 2009-017346-32	Primary: <ol style="list-style-type: none"> To evaluate the safety of the administration of autologous CD34+ cells transduced with an LVV containing the WAS gene (WASKYRA) in patients with WAS, after a reduced intensity conditioning regimen To evaluate the long-term engraftment of WASP-expressing transduced cells To evaluate the efficacy of gene therapy assessed as: <ol style="list-style-type: none"> Improvement of the patient's immune function, specifically of T- cell function and antigen-specific responses to vaccinations Improvement of thrombocytopenia Secondary: <ol style="list-style-type: none"> To evaluate the efficacy of gene therapy in improving the patient's clinical conditions, assessed by reduction in frequency of severe infections, bleeding episodes, and reduction of autoimmunity phenomena and eczema 	Phase I/II, open-label, single- arm, non-randomized, prospective, single-center study using the 12-month pre-treatment period as comparator	WASKYRA (etuvetidigene autotemcel; previously known as GSK2696275 and OTL-103; fresh formulation) Cell source ^a for DP manufacturing: BM (n=5) Cryopreserved mPB (n=2) BM and cryopreserved mPB (n=1) IV infusion; single dose Autologous use	Eight (eight enrolled ^a , eight treated); with a median age of 2.2 years (range 1.1-12.4 years)	Completed

Study Identifier	Objective(s)	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients Treated	Study Status
OTL-103-4 NCT038374831 EudraCT 2018-003842-18	Primary: 1. To evaluate the clinical efficacy of the cryopreserved formulation of WASKYRA at 12 months for bleeding events and from 6–18 months for severe infections Secondary: To evaluate: 1. Overall survival at 12, 24, and 36 months 2. Safety of treatment with WASKYRA 3. Engraftment at 6 months 4. Biological efficacy of the cryopreserved formulation of WASKYRA at 12 months, 2 years, and 3 years 5. Clinical efficacy of the cryopreserved formulation of WASKYRA at 2 and 3 years 6. Sustained engraftment of the cryopreserved formulation of WASKYRA at 2 and 3 years 7. Immunological function after treatment with WASKYRA up to 3 years 8. Effect of WASKYRA on health-related quality of life at 2 and 3 years 9. Exploratory: 10. To evaluate: 11. Safety of treatment with WASKYRA 12. Effect of WASKYRA on health-related quality of life at 1, 2, and 3 years 13. Effect of WASKYRA on platelet function	An open-label, single- arm, non-randomized, multi-center study using the 12- month pre-treatment period as comparator	WASKYRA (also known as GSK2696275 and OTL-103; cryopreserved formulation) Cell source ^b for DP <u>manufacturing</u> : Fresh mPB (n=10) IV infusion; single dose Autologous use	Ten (10 enrolled, 10 treated) with a median age of 2.0 years (range 1.0 – 9 years)	Ongoing
Expanded Access Program (HE 205030; CUP 206257)	To provide treatment for patients affected by WAS with high unmet medical need in advance of the product being commercially available, in line with the principles of GCP and according to the Italian Ministerial Decree of January 16, 2015 (for HE patients) or Ministerial Decree of September 7, 2017 (superseding decree dated May 8, 2003 [for CUP patients])	A prospective, single-center treatment program in patients with WAS (Patients treated with WASKYRA at Ospedale San Raffaele in Milan)	WASKYRA (also known as GSK2696275 and OTL-103; fresh formulation) Cell source ^b for DP <u>manufacturing</u> : cryopreserved mPB (n=9) IV infusion; single dose Autologous use	Overall: 10 enrolled, nine treated (HE: three enrolled and treated CUP ^c : seven enrolled, six treated) with a median age of 3.8 years (range 1.4 – 35.1 years)	Completed

Study Identifier	Objective(s)	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients Treated	Study Status
		[Italy] under the provisions of HE/Compassionate Use)			

Source: Adapted from BLA 125846, Summary of Clinical Safety, Table 1

^a An additional patient (b) (6) provided informed consent but met an exclusion criterion and was considered a screening failure, and thus was not treated (see TIGET-WAS Clinical Study Report [CSR], Module 5).

^b Cell source refers to how CD34+ cells were harvested: from BM directly via an aspirate, or apheresis for mobilized CD34+ cells (mPB) for DP manufacture.

^c One patient did not receive the conditioning regimen or WASKYRA as an insufficient number of mobilized CD34+ cells were harvested for obtaining the minimum target dose of CD34+ cells required for DP manufacturing.

^d Evaluation of immune response to WAS transgene.

Abbreviations: BM, bone marrow; CD, cluster of differentiation; CUP, Compassionate Use Program; DP, drug product; GCP, Good Clinical Practice; HE, Hospital Exemption; IV, intravenous; LVV, lentiviral vector; mPB, mobilized peripheral blood; WAS, Wiskott-Aldrich syndrome; WASP, Wiskott-Aldrich syndrome protein

Reviewer Comment: *Study TIGET-WAS was a foreign clinical study and not conducted under an IND. Per 21 CFR 312.120, the study is acceptable as it was conducted in accordance with good clinical practice and FDA was able to conduct BIMO site inspection (see the BIMO memo for details). The BLA contained primarily data outside of the United States, which are considered applicable to the U.S. population and U.S. medical practice for WAS.*

5.5 Literature Reviewed (if applicable)

1. Albert, MH, MA Slatter, AR Gennery, T Güngör, K Bakunina, B Markovitch, S Hazelaar, T Sirait, V Courteille, A Aiuti, OV Aleinikova, D Balashov, ME Bernardo, I Bodova, B Bruno, M Cavazzana, R Chiesa, A Fischer, F Hauck, M Ifversen, K Kalwak, C Klein, A Kulagin, A Kupesiz, B Kuskonmaz, CA Lindemans, F Locatelli, SH Lum, A Maschan, R Meisel, D Moshous, F Porta, MG Sauer, P Sedlacek, A Schulz, F Suarez, TC Vallée, JH Winiarski, M Zecca, B Neven, P Veys, and AC Lankester, 2022, Hematopoietic stem cell transplantation for Wiskott-Aldrich syndrome: an EBMT Inborn Errors Working Party analysis, *Blood*, 139(13):2066-2079.
2. Bosticardo, M, F Marangoni, A Aiuti, A Villa, and M Grazia Roncarolo, 2009, Recent advances in understanding the pathophysiology of Wiskott-Aldrich syndrome, *Blood*, 113(25):6288-6295.
3. Buchbinder, D, DJ Nugent, and AH Fillipovich, 2014, Wiskott-Aldrich syndrome: diagnosis, current management, and emerging treatments, *Appl Clin Genet*, 7:55-66.
4. Burroughs, LM, A Petrovic, R Brazauskas, X Liu, LM Griffith, HD Ochs, JJ Bleesing, S Edwards, CC Dvorak, S Chaudhury, SE Prockop, R Quinones, FD Goldman, TC Quigg, S Chandrakasan, AR Smith, S Parikh, BJ Dávila Saldaña, MS Thakar, R Phelan, S Shenoy, LR Forbes, C Martinez, D Chellapandian, E Shereck, HK Miller, N Kapoor, JL Barnum, H Chong, DC Shyr, K Chen, R Abu-Arja, AJ Shah, KG Weinacht, TB Moore, A Joshi, KB DeSantes, AP Gillio, GDE Cuvelier, MD Keller, J Rozmus, T Torgerson, MA Pulsipher, E Haddad, KE Sullivan, BR Logan, DB Kohn, JM Puck, LD Notarangelo, SY Pai, DJ Rawlings, and MJ Cowan, 2020, Excellent outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome: a PIDTC report, *Blood*, 135(23):2094-2105.
5. Dupuis-Girod, S, J Medioni, E Haddad, P Quartier, M Cavazzana-Calvo, F Le Deist, G de Saint Basile, J Delaunay, K Schwarz, JL Casanova, S Blanche, and A Fischer, 2003, Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients, *Pediatrics*, 111(5 Pt 1):e622-627.
6. Glasmacher, JS, TC Bittner, HD Ochs, A Aiuti, PD Arkwright, D Balashov, U Behrends, BH Belohradsky, E Bertoni, DK Buchbinder, M Browning, A Bondarenko, F Candotti, A Cattoni, L Chernyshova, JH Chewning, P Ciznar, T Cole, BT Costa-Carvalho, W Czogala, G Dueckers, DM Edgar, F Erbey, A Fasth, R Formankova, T Freiburger, E Gambineri, A Gennery, FD Goldman, LI Gonzalez-Granado, TN Gulmaraes, D Hagin, F Hauck, T Heiskanen-Kosma, M Hoenig, H Juntti, H Kanegane, L Kainulainen, NE Karaca, SS Kilic, C Klein, S Koltan, I Kondratenko, D Liu, S Matthes, JTL Mazzucchelli, I Meyts, S Misbah, Z Nademi, G Nasrullayeva, LD Notarangelo, P Soler-Palacin, O Pashchenko, S Pasic, I Pellier, C Pignata, C Roepstorff, C Schuetz, AS Schulz, GRS Segundo, A Shcherbina, J Smart, RA Sokolic, P Stepensky, T Torgerson, S Vakhlyarskaya, J van Montfrans, K Vettenranta, B Wolska-Kusnierz, X Zhao, JB Ziegler, X Zhang, and MH Albert, 2016, Wiskott-Aldrich Syndrome: A Retrospective Study on 575 Patients Analyzing the Impact of Splenectomy, Stem Cell Transplantation, or No Definitive Treatment on Frequency of Disease-Related Complications and Physician-Perceived Quality of Life, *Blood*, 128(22):366-366.

7. Jin, Y, C Mazza, JR Christie, S Giliani, M Fiorini, P Mella, F Gandellini, DM Stewart, Q Zhu, DL Nelson, LD Notarangelo, and HD Ochs, 2004, Mutations of the Wiskott-Aldrich Syndrome Protein (WASP): hotspots, effect on transcription, and translation and phenotype/genotype correlation, *Blood*, 104(13):4010-4019.
8. Lankester, AC, MH Albert, C Booth, AR Gennery, T Güngör, M Hömig, EC Morris, D Moshous, B Neven, A Schulz, M Slatter, and P Veys, 2021, EBMT/ESID inborn errors working party guidelines for hematopoietic stem cell transplantation for inborn errors of immunity, *Bone Marrow Transplant*, 56(9):2052-2062.
9. Magnani, A, M Semeraro, F Adam, C Booth, L Dupré, EC Morris, A Gabrion, C Roudaut, D Borgel, A Toubert, E Clave, C Abdo, G Gorochoy, R Petermann, M Guiot, M Miyara, D Moshous, E Magrin, A Denis, F Suarez, C Lagresle, AM Roche, J Everett, A Trinquand, M Guisset, JX Bayford, S Hacein-Bey-Abina, A Kauskot, R Elfeky, C Rivat, S Abbas, HB Gaspar, E Macintyre, C Picard, FD Bushman, A Galy, A Fischer, E Six, AJ Thrasher, and M Cavazzana, 2022, Long-term safety and efficacy of lentiviral hematopoietic stem/progenitor cell gene therapy for Wiskott-Aldrich syndrome, *Nat Med*, 28(1):71-80.
10. Ochs, HD and AJ Thrasher, 2006, The Wiskott-Aldrich syndrome, *J Allergy Clin Immunol*, 117(4):725-738; quiz 739.
11. Sereni, L, MC Castiello, D Di Silvestre, P Della Valle, C Brombin, F Ferrua, MP Cicalese, L Pozzi, M Migliavacca, ME Bernardo, C Pignata, R Farah, LD Notarangelo, N Marcus, L Cattaneo, M Spinelli, S Giannelli, M Bosticardo, K van Rossem, A D'Angelo, A Aiuti, P Mauri, and A Villa, 2019, Lentiviral gene therapy corrects platelet phenotype and function in patients with Wiskott-Aldrich syndrome, *J Allergy Clin Immunol*, 144(3):825-838.
12. Vallée, TC, JS Glasmacher, H Buchner, PD Arkwright, U Behrends, A Bondarenko, MJ Browning, D Buchbinder, A Cattoni, L Chernyshova, P Ciznar, T Cole, W Czogała, G Dueckers, JDM Edgar, F Erbey, A Fasth, F Ferrua, R Formankova, E Gambineri, AR Gennery, FD Goldman, LI Gonzalez-Granado, C Heilmann, T Heiskanen-Kosma, H Juntti, L Kainulainen, H Kanegane, NE Karaca, SS Kilic, C Klein, S Koltan, I Kondratenko, I Meyts, GM Nasrullayeva, LD Notarangelo, S Pasic, I Pellier, C Pignata, S Misbah, A Schulz, GR Segundo, A Shcherbina, M Slatter, R Sokolic, P Soler-Palacin, P Stepensky, JM van Montfrans, S Ryhänen, B Wolska-Kuśnierz, JB Ziegler, X Zhao, A Aiuti, HD Ochs, and MH Albert, 2024, Wiskott-Aldrich syndrome: a study of 577 patients defines the genotype as a biomarker for disease severity and survival, *Blood*, 143(24):2504-2516.
13. *Externally-Led Patient Focused Drug Development on Wiskott-Aldrich Syndrome (WAS) and X-Linked Thrombocytopenia (XLT) Voice of the Patient Report* (Wiskott-Aldrich Foundation 2023)
14. Zhu, Q, C Watanabe, T Liu, D Hollenbaugh, RM Blaese, SB Kanner, A Aruffo, and HD Ochs, 1997, Wiskott-Aldrich syndrome/X-linked thrombocytopenia: WASP gene mutations, protein expression, and phenotype, *Blood*, 90(7):2680-2689.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: A Phase 1/2 Clinical Trial of Hematopoietic Stem Cell Gene Therapy for the Wiskott-Aldrich Syndrome (TIGET-WAS/201228)

NCT01515462

6.1.1 Objectives (Primary, Secondary, etc)

Primary

1. To evaluate the safety of the administration of autologous CD34+ cells transduced with an LVV containing the WAS gene (WASKYRA) in patients with WAS, after an RIC regimen
2. To evaluate the long-term engraftment of WASP-expressing transduced cells
3. To evaluate the efficacy of GT assessed as:
 - a) Improvement of the patient's immune function, specifically of T-cell function and antigen-specific responses to vaccinations
 - b) Improvement of thrombocytopenia

Secondary

To evaluate the efficacy of GT in improving the patient's clinical conditions, assessed by reduction in frequency of severe infections, bleeding episodes, and reduction of autoimmunity phenomena and eczema

6.1.2 Design Overview

TIGET-WAS (201228) was a Phase 1/2, open-label, single-arm, nonrandomized, prospective, single-center study using the 12-month pre-treatment period as comparator.

The study was conducted in five distinct phases:

1. Screening
2. Baseline: This phase extended from the end of screening to the day before either PB stem cell harvest (if performed) or Rituximab administration (Day -22).
3. Treatment: This phase spanned from baseline to Day 0.
4. Follow-up: This phase consisted of two parts:
 - a) An initial follow-up period of at least 3 years, during which patients were expected to reach the primary efficacy analysis timepoint.
 - b) A subsequent long-term follow-up period extending from 3 to 8 years.
5. Extended long-term follow-up: After completing the follow-up phase, patients were contacted annually until they transitioned to a separate, observational, long-term follow-up study. Patients became eligible for the observational long-term follow-up after a minimum of 5 years of follow-up in the main study.

6.1.3 Population

The key eligibility criteria were as follows:

Inclusion Criteria

1. Diagnosis of WAS, defined by genetic mutation and at least one of the following criteria: severe clinical score (Zhu clinical score ≥ 3), severe WAS mutation, or absent WASP expression.
 - a. The severity of the genetic mutation was defined by literature data (genotype-phenotype studies), database information, and prediction studies, and the level of residual WASP expression was assessed by fluorescence activated cell sorting analysis in PB lymphocytes.
 - b. Expression of WASP was classified as present if $>20\%$, reduced if $<20\%$, and absent if $<5\%$. The presence of a cell population expressing normal levels of WASP and representing $>5\%$ of lymphocytes was classified as revertant.
2. No HLA-identical sibling donor AND negative search for a matched unrelated donor (10/10) or an adequate unrelated cord blood donor (6/6) within 4 to 6 months OR Patients >5 years who were not candidates for unrelated allogeneic transplant based on clinical condition.
 - a) The identification of a matched unrelated donor was established based on high resolution allele-level DNA matching for 10/10 alleles (HLA-A, -B, -C, -DRB, and -DQB1 loci). For umbilical cord blood transplantation, both cell dose ($>2.5 \times 10^7$ nucleated cells/kg body weight) and HLA matching (low-resolution HLA-A, -B, and high-resolution DRB1) were considered.
3. Parental/guardian/patient signed informed consent.

Exclusion Criteria

1. Patients positive for HIV-1 infection
2. Patients affected by neoplasia
3. Patients with cytogenetic alterations typical of myelodysplastic syndromes/acute myeloid leukemia
4. Patients with end-organ functions or any other severe disease which, in the judgment of the investigator, would have made the patient inappropriate for entry into this study
5. Patients who had undergone an allogeneic HSCT in the previous 6 months
6. Patients who had undergone an allogeneic HSCT with evidence of residual cells of donor origin

An exclusion criterion related to revertant expression of WASP in $>5\%$ of lymphoid cells was removed in Protocol Version 6.0.6.1.4 Study Treatments or Agents Mandated by the Protocol

6.1.4 Study Treatments

The protocol mandated specific treatments for different study phases, including collection of back-up cells, BM harvest for cells to be transduced, RIC using rituximab, busulfan, and fludarabine, and infusion of transduced CD34+ cells. Prior to initiating any study procedures, a central venous catheter was placed under general anesthesia.

Mobilization of CD34+ Cells

Granulocyte-colony stimulating factor (G-CSF, 10-12.5 mcg/kg in 2 divided doses) was administered per protocol. Starting from Day 3 of G-CSF administration, Plerixafor was administered to enhance peripheral blood stem cell mobilization. The starting day of the Plerixafor administration could be shifted to Day 4 or 5 depending on white blood cell and CD34+ cell count/mcl in the patient's PB. Patients received Plerixafor once daily at the dose of 0.24 mg/kg subcutaneously approximately 8 to 10 hours before standard leukapheresis was performed. G-CSF and Plerixafor administration was repeated until sufficient mPB CD34+ cells were harvested (up to a maximum of 3 leukapheresis on 3 consecutive days or 7 days of G-CSF administration).

Reduced Intensity Conditioning

Reduced intensity conditioning was selected based on the assumption that a stable mixed chimerism with gene corrected and uncorrected cells, both in BM and PB, could be sufficient to provide clinical benefit, with a reduced regimen-related toxicity.

The RIC regimen consisted of three components administered intravenously. Rituximab was given as a single dose of 375 mg/m² on Day -22. Busulfan was administered in eight (\pm one) doses every 6 hours from Days -3 to -1, with the dose adjusted based on pharmacokinetic monitoring to achieve a target cumulative area under the curve (AUC) of 48,000 \pm 10% ng/mL*h. The initial target AUC range was 36,000 to 48,000 ng/mLh. After six patients had been treated, the protocol was amended to set a narrower target AUC of 48,000 \pm 10% ng/mLh, as data suggested that lower exposure might be associated with reduced myeloid engraftment and prolonged platelet transfusion dependence. Fludarabine was given at a total dose of 60 mg/m², split into two doses on Days -3 and -2.

6.1.5 Directions for Use

Patients were admitted to an isolation unit in a pediatric transplant center for the procedure. Prior to infusion, patients received premedication with chlorpheniramine (0.25 mg/kg, maximum dose 10 mg) 15 to 30 minutes before the procedure. The transduced cells were then infused intravenously through a central venous catheter over a period of 20 minutes. Each patient received a dose of transduced CD34+ cells ranging from 2 to 20 \times 10⁶ cells/kg.

6.1.6 Sites and Centers

This was a single-site study conducted at Ospedale San Raffaele in Milan, Italy. A full list of investigators was provided by the Applicant in the appendices of module 5 (16.1.4).

6.1.7 Surveillance/Monitoring

Patients were actively monitored in this study until Year 3 on Days 7, 14, 21, 30, 60, 90, and 180, then every 6 months until Year 3. Patients were then followed annually as part of a long-term follow-up over Years 4 to 8. An extended long-term-follow-up period began after Year 8.

Safety assessments included:

- Clinical examination: anamnesis, physical examination with assessment of performance status by Lansky Play-Performance Scale, and eczema assessment by Life Measurement Instrument Assessment (LMAI).

- Zhu score.
- WASP expression, assessed by fluorescence-activated cell sorting (FACS) analyses on PB.
- Specialist examinations: cardiological, immunological, ophthalmological.
- Diagnostic imaging and instrumental tests, Imaging n°1: chest X-ray, electrocardiogram (ECG), abdomen ultrasound scan, echocardiogram, Rx of left hand-wrist for evaluation of bone age, respiratory functional test (if children older than 5 years old). Imaging n°2: chest computed tomography scan. Imaging n°3: ECG, abdomen ultrasound scan, echocardiogram, Rx of left hand-wrist for evaluation of bone age, respiratory functional test (if children older than 5 years old). In addition, at fifth year: chest X-ray or computed tomography scan if clinical indication, and at eighth year: chest computed tomography scan. Imaging n°4: ECG, abdomen ultrasound scan, echocardiogram, respiratory functional test (if children older than 5 years old).
- Routine laboratory n°1: complete blood count with differential (absolute count), including platelet count, mean platelet volume (MPV, every year), C-reactive protein, lactate dehydrogenase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, blood glucose, blood urea nitrogen, creatinine, creatine phosphokinase, alkaline phosphatase, gamma-glutamyl transferase, electrolytes, protein content, urinalysis. Routine laboratory n°2: erythrocyte sedimentation rate, protein electrophoresis, blood iron, transferrin, ferritin, reticulocytes, blood gases analyses, thyroid balance, coagulation (XDP, PT, activated partial thromboplastin time, fibrinogen).
- Bone marrow evaluation: needle aspirate with immunophenotype: CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD20+, CD22+, CD20+/CD22+, CD2+, CD16+/CD56+, CD19+/IgM+, CD19+/kappa, CD19+/lambda, CD71+/Glycophorin A+, CD15+, CD13+, CD38+/CD138+, CD61+, CD34+(ISHAGE), clonogenic progenitors (colony-forming unit-culture), morphology, and karyotype. Polymerase chain reaction (PCR) analysis on transduced cells was performed separately, including the assessment of %LV+ colony-forming cells from patient's BM-derived clonogenic progenitors.
- Microbiological evaluation: n°1: Search for bacteria and fungi in nasal and pharyngeal swabs; cytomegalovirus and Epstein–Barr virus DNA search by molecular tests on PB plasma, stool culture, search for bacteria in the urine. N°2: Search for *Legionella* antigen in urine. Search for Bacteria, Mycobacteria, fungi, *Pn. jirovecii*, *Legionella*, *Chlamydia pn.* and *Mycoplasma pn.* in deep pharyngeal aspirates. Search for Respiratory Syncytial Virus in nasal wash. Search for adenovirus in the blood (molecular test); search for parasites and enteroviruses in the stools. N°3 Search for herpes simplex virus type 1, herpes simplex virus type 2, Human herpes virus 6, Human herpes virus 7, Hepatitis C virus, Hepatitis B virus, HIV genomes in the PB plasma (molecular test).
- Immunological evaluation n°1: Immunophenotype with lymphocyte subpopulations (CD45+, CD14+, CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD2+, CD16+/CD56+, percentage and absolute count. Serum immunoglobulins (IgG, IgA, IgM, total IgE). n°2: Immunophenotype with lymphocyte subpopulations (CD3+, CD4+, CD8+, CD16+, CD56+, CD14+, CD45+, T-cell receptor (TCR)1+ (alfa/beta), TCR2+ (gamma/delta), CD4+/CD45RA+ & CD45RO+, CD8+/CD45RA+ & CD45RO+, CD4+/DR+, CD8+/DR+, CD4+/CD25+, CD8+/CD25+, CD3+/CD4+, CD3+/CD8+, CD19+, CD2+, CD16+/CD56+, kappa+, lambda+) percentage and absolute count. Serum immunoglobulins (IgG, IgA, IgM, total IgE). n°3: Proliferative response to mitogens (phytohemagglutinin, anti-immobilized CD3 (CD3i), anti-CD3i+anti-CD28, IL-2, pokeweed mitogen). n°4: Proliferative response to *Candida* and alloantigens. Proliferative response to tetanus toxoid (if patient was vaccinated). Dose response of proliferation after anti-CD3i

stimulation on PB mononuclear cells and/or T-cell lines. TCR repertoire studies in the PB by FACS (Vbeta repertoire). n°5: In patients who discontinued intravenous Ig, a vaccination program was started. Serum antibody levels to vaccinal antigens (tetanus toxoid, diphtheria, hepatitis B, *Pneumococcus*, Pertussis, *Hemophilus B*) or pathogens (EBV viral capsid antigen, cytomegalovirus, measles, rubeola, Varicella zoster virus, herpes simplex virus) were measured.

- Autoimmunity evaluation, searching organ-specific and systemic antibodies in the serum: anti-platelet antibodies, anti-nuclear antibodies; anti-extractable nuclear antigens antibodies, if anti-nuclear antibody positive; anti-neutrophil cytoplasmic antibodies (p-ANCA, c-ANCA); anti-DNA antibodies; anti-mitochondrial antibodies; anti smooth muscle antibodies, anti-Liver-Kidney-Muscle; Coombs' tests (direct/indirect).
- Evaluation of the presence of genetically modified cells. Vector copy number (measured by quantitative PCR as VCN/cells) was done after GT in total nucleated cells (Day +14), and afterwards in PB lymphocyte subpopulations (CD3+ and/or CD4+ and CD8+ T lymphocytes, B lymphocytes, natural killer cells) and granulocytes and in BM cell subpopulations (CD15+, GlyA+, CD3+, CD19+, CD56+, CD34+).
- Archiving of samples. Samples from PB and BM (serum, plasma, cell pellets, viable cells in DMSO, cell lines, DNA) were archived and stored at -80° at San Raffaele Telethon Institute for Gene Therapy, according to Institutional guidelines.
- Platelet activation and morphology: For platelet activation, the expression of activation markers on the surface of PB-derived platelets after stimulation with agonists was assessed. For platelet morphology, the platelet perimeter, area, and ultrastructure were assessed by transmission electron microscopy.
- Replication-competent lentivirus (RCL) monitoring.
- Abnormal clonal proliferation monitoring.
- Antibodies anti-WASP, anti-HIV.

6.1.8 Endpoints and Criteria for Study Success

Primary Safety Endpoints

1. Hematological reconstitution

The safety of the RIC regimen associated with the infusion of ex vivo transduced CD34+ cells was demonstrated by the absence of engraftment failure and prolonged aplasia, defined as absolute neutrophil count (ANC) <500/ μ L at Day +60 without evidence of BM recovery or need for backup cell administration.

2. Regimen-related nonhematopoietic toxicity

Clinical and laboratory parameters were monitored for the first 100 days post-transplant using CTCAE criteria (\geq Grade 2 for clinical features, \geq Grade 3 for metabolic/laboratory findings) to assess morbidity associated with the reduced conditioning regimen.

3. Short-term safety and tolerability of lentiviral-transduced cell infusion

Evaluated by monitoring AEs and systemic reactions (fever, tachycardia, nausea, joint pain, skin rash) within 48 hours of infusion, with an emphasis on the absence of serious adverse reactions during this period.

Efficacy Endpoints

1. **Overall Survival:** From Day +1 to 3 years after GT, and then monitored as part of the long-term follow up.
2. **Sustained engraftment of genetically corrected hematopoietic stem cells in PB and/or BM:** Adequate engraftment was defined as ≥ 0.04 VCN/cell in BM CD34+ (equivalent to 4% assuming a VCN of 1) or ≥ 0.1 VCN/cell in PB T lymphocytes (equivalent to 10% assuming a VCN of 1).
3. **Expression of vector-derived WASP:** Presence of detectable vector-derived WASP expression at 1 year after GT by FACS analyses and/or Western Blot.
4. **Improved T-cell function:** Improvement in in vitro T-cell proliferation upon stimulation with anti-CD3i mAbs at 1, 2, and 3 years after GT as compared to pre-GT values.
5. **Antigen-specific responses to vaccinations:** A vaccination program was initiated once each patient had discontinued IgRT (at least 3 months after the last Ig supplementation) and their immunological status was considered to be sufficiently improved.
 - a. Antibody responses were tested following the administration of protein-based vaccines against Tetanus Toxoid, Diphtheria, Hepatitis B, Pertussis, Haemophilus B, or polysaccharide-protein conjugated or unconjugated vaccines against Pneumococcus. A positive response was defined as the presence of antibodies to at least 4 out of 5 T-cell dependent antigens measured after the end of the vaccination schedule, or at least n-1 if fewer than five antigens were tested.
 - b. Positive cellular response to Tetanus Toxoid after vaccination, measured by in vitro proliferative response >1 year after GT.
6. **Improved platelet count and normalization of MPV at 1 year:**
 - a. Sustained increase in platelet count compared to baseline during the 3-year follow up.
 - b. Patients were also stratified according to the severity of thrombocytopenia before GT, and the patient was defined as improved if there was a shift from one group to the subsequent.

Secondary Efficacy Endpoints

1. Longitudinal analyses of sustained engraftment of genetically corrected HSPCs in PB and/or in BM and expression of vector-derived WASP
2. Analyses of sustained multilineage engraftment of genetically corrected cells in PB and/or in BM
3. Reduced frequency of severe infections
4. Reduced bleeding episodes
5. Reduced autoimmunity phenomena and eczema: manual review of clinical events conducted by investigators to identify events of autoimmunity due to absence of a MedDRA SMQ grouping
6. Improved quality of life

Exploratory Endpoints

Efficacy

Platelet activation profile and morphology

Retrospective Collection of Pre-Treatment Events

For all patients enrolled in the study, the investigators collected a full medical history along with a review of the referring physician's medical notes, including summaries from the referring healthcare providers, results of diagnostic tests, discharge letters from hospitals, and any other additional, medically relevant information to document medical events, hospitalizations, diagnostic procedures including imaging and tests, surgical procedures, and treatments.

The documentation was then used as follows:

- A list of the documented medical events reported in the documentation was recorded in the Case Report Form (CRF) as Relevant Medical History and Relevant Previous Treatment at screening. The original source kept on file and summarized by the screening physician in the clinical notes.
- Copies of diagnostic tests performed were filed in the clinical notes as source documents and used to support the diagnosis and severity of the events reported in the CRF.
- Details of the treatments administered, including antimicrobials, Igs, and platelet transfusions, were recorded in the concomitant Medication section of the CRF. The information was used to define the severity of the events. Supporting documentation were filed in the clinical notes as source documents.
- The medical history was supplemented with additional anamnestic information collected from the patient and/or their caregivers at the screening visit. The clinical history was carefully recorded in the clinical notes as a narrative by the screening physicians and the information checked against the records available as per previous points. Any new undocumented medical information collected through the anamnesis was recorded in the CRF as relevant Medical History.

Prospective Collection of Pre-Treatment Events

After enrollment, new infections, bleeding events, and other relevant medical events were recorded prospectively in the CRF as "Concomitant Disease" until WASKYRA administration (which included the period of apheresis or BM collection and conditioning), and as "Adverse Events" thereafter. Infections and bleeding episodes were diagnosed based on documented clinical evidence. Bleeding information was collected from parents, local doctors' reports, and follow-up visits at the investigator site.

Severity Assessment of the Pre-Treatment Events

The severity of the infection and bleeding events was assigned by the investigators using the CTCAE definitions. Grade 1 and Grade 2 events were respectively considered as mild and moderate (limited age-appropriate instrumental activities of daily living). An event of Grade 3 or above was considered severe. Events of Grade 4 were considered "life-threatening" and/or urgent intervention was indicated.

For bleeding:

- Grade 1: no treatment indicated
- Grade 2: intervention indicated
- Grade 3: event requires platelets or red blood cells transfusions; and/or invasive intervention; and/or hospitalization
- Grade 4: life-threatening consequences, and/or urgent intervention indicated
- Grade 5: death

For infections:

- Grade 3: an event requiring intravenous antibiotics; and/or antifungal intervention; and/or antiviral intervention and/or invasive intervention
- Grade 4: life-threatening consequences and/or urgent intervention
- Grade 5: death

CTCAE grading was consistently applied to both retrospectively collected pre-treatment events and prospectively collected post-screening events. For infections or bleeding events not specifically listed in CTCAE, clinical judgment was used for grading.

6.1.9 Statistical Considerations & Statistical Analysis Plan

See the statistical reviewer's memorandum for discussion of the statistical analysis plan.

An integrated analysis of efficacy is discussed in section [7.1.4](#).

6.2 Trial # 2: A Single-Arm, Open-Label Clinical Study of Hematopoietic Stem Cell Gene Therapy with Cryopreserved Autologous CD34+ Cells Transduced with Lentiviral Vector encoding WAS Complementary DNA in Patients with Wiskott Aldrich Syndrome

NCT03837483

Reviewer Comment: *This study protocol shares many similarities with Study TIGET-WAS, and Study OTL-103-4 was conducted to study the cryopreserved formulation of WASKYRA, which is intended as the commercial product. This cryopreserved formulation extends the shelf-life of WASKYRA. Only the key study design features and differences between Studies TIGET-WAS and OTL-103-4 will be highlighted in this section.*

6.2.1 Objectives (Primary, Secondary, etc)

Primary

To evaluate the clinical efficacy of the cryopreserved formulation of WASKYRA at 12 months for bleeding events and from 6 to 18 months for severe infections

Secondary

1. To evaluate the OS at 12, 24, and 36 months
2. To evaluate the safety of treatment with WASKYRA
3. To evaluate the engraftment at 6 months
4. To evaluate the biological efficacy of the cryopreserved formulation of WASKYRA at 12 months, 2 years, and 3 years

5. To evaluate the clinical efficacy of the cryopreserved formulation of WASKYRA at 2 and 3 years
6. To evaluate sustained engraftment of the cryopreserved formulation of WASKYRA at 2 and 3 years
7. To evaluate the immunological function after treatment with WASKYRA up to 3 years
8. To evaluate the effect of WASKYRA on health-related quality of life at 2 and 3 years

Exploratory

1. To evaluate the safety of treatment with WASKYRA
2. To evaluate the effect of WASKYRA on health-related quality of life at 1, 2, and 3 years
3. To evaluate the effect of WASKYRA on platelet function

6.2.2 Design Overview

OTL-103-4 is an open-label, single-arm, nonrandomized, multicenter study using the 12-month pre-treatment period as comparator that started on January 21, 2019. The last patient was treated on September 26, 2022. The study is ongoing. An interim CSR was issued on September 19, 2024, with a data cut-off date of December 4, 2023.

6.2.3 Population

The key eligibility criteria were as follows:

Main Inclusion Criteria

1. Diagnosis of WAS defined by genetic mutation and at least one of the following criteria:
 - a. Severe WAS mutation, defined by literature data, database information, and prediction studies (genotype/phenotype studies)
 - b. Absent WASP expression, assessed by flow cytometry
 - c. Severe clinical score (Zhu clinical score ≥ 3)
2. No HLA-identical related donor available for HSCT

Exclusion Criteria

1. End-organ dysfunction, severe active infection not responsive to treatment or other severe disease or clinical condition which, in the judgment of the investigator, would make the patient inappropriate for entry into this study
2. Malignant neoplasia (except local skin cancer) or a documented history of hereditary cancer syndrome. Patients with a prior successfully treated malignancy and sufficient follow-up to exclude recurrence (based on oncologist opinion) could be included after discussion and approval by the Medical Monitor
3. Myelodysplasia, cytogenetic alterations characteristic of myelodysplastic syndrome and acute myeloid leukemia, or other serious hematological disorders
4. Prior allogeneic HSCT, with evidence of residual cells of donor origin
5. Documented HIV infection (positive HIV RNA and/or anti-p24 antibodies)
6. Previous GT

6.2.4 Study Treatments or Agents Mandated by the Protocol

1. Mobilization of CD34+ cells:
High doses of G-CSF were administered twice daily (total dose of 10-12.5 $\mu\text{g/kg}$, administered in two divided doses) to increase mobilization of CD34+ cells from the BM

into PB. On the fourth and fifth days of G-CSF administration, an additional mobilizing agent, plerixafor, was administered subcutaneously once daily at a dose of 0.24 mg/kg, approximately 6 to 8 hours before each standard leukapheresis session.

2. Reduced conditioning regimen:

- Rituximab was administered intravenously on Day -22 (± 1 day), prior to the conditioning regimen, in a single dose of 375 mg/m².
- Fludarabine (intravenous): two single doses of 30 mg/m²/day, on Day -4 and Day -3, respectively
- Busulfan (intravenous) body weight-based and AUC-targeted dose (dose range: 0.8-1.2 mg/kg/dose).
 - Eight doses were administered every 6 hours from Day -4 to Day -2.
 - If the target AUC was not achieved with eight doses, additional doses were administered every 6 hours, based on AUC measurements.
 - The cumulative target AUC was 48,000 ng/mL·h $\pm 10\%$.
 - Dosing was stopped if the target AUC was reached before the eighth dose.
 - Busulfan dosing was stopped at least 24 hours before the infusion of WASKYRA.

6.2.5 Directions for Use

The directions for use for OTL-103 are similar to that for Study TIGET-WAS. However, the recommended drug product dose is 3 to 30 $\times 10^6$ CD34+ cells/kg. As per Study TIGET-WAS, the actual dose was dependent on the yield of cells available after transduction. Please see [Section 6.1.5](#).

6.2.6 Sites and Centers

The study was primarily conducted at the Pediatric Clinical Research Unit/Pediatric Immunohematology and Bone Marrow Transplantation Unit in Ospedale San Raffaele, Milan, Italy (n=9). One patient was enrolled at the Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA 30322, United States.

6.2.7 Surveillance/Monitoring

The schedule of assessments did not differ significantly from that of Study TIGET-WAS. Please see [Section 6.1.7](#).

6.2.8 Endpoints and Criteria for Study Success

Collection of Baseline Events

Similar to during Study TIGET-WAS, investigators received documentation from local healthcare providers that included, but was not limited to, medical summaries, reports, letters from the referring physicians, and discharge letters and hospital notes from inpatient and outpatient services who had followed the patient, documenting medical events, hospitalizations, diagnostic procedures, including imaging and laboratory tests, surgical procedures, and treatments the patient had in his history. Overall, the documentation collected was meant to cover the whole medical history of the patient from birth in as much detail as possible. The documented medical events reported in the pre-treatment documentation were recorded in the electronic Case Report Form (eCRF) as Relevant Medical History at screening. At screening, additional anamnestic information was collected from the patient and/or the carers to supplement the

medical history. The anamnesis was recorded in the clinical notes as a narrative, and the information was checked against the records available. Any new, undocumented medical information collected through the anamnesis was recorded in the eCRF as relevant Medical History.

Reviewer Comment: *A separate protocol for baseline history collection was not made; rather, this is an excerpt from the OTL-103-4 protocol on collection of data for pre-treatment events. In response to Information Request #22, received on June 6, 2025, the Applicant reported that additional undocumented anamnestic medical information from caregivers was limited, primarily concerning remote past events, mild home-managed incidents, or those treated with over-the-counter medications. For most medically relevant events, including severe infections and moderate/severe bleeding, documented medical records or healthcare provider communications were available.*

Primary Efficacy (Co-Primary Endpoints)

- Annualized rate of severe infections from 6 to 18 months after WASKYRA compared with 1 year prior to WASKYRA
- Annualized rate of moderate and severe bleeding episodes up to 1 year after WASKYRA compared with 1 year prior to WASKYRA

Secondary Efficacy

- Overall survival
- Hematological reconstitution and engraftment
- Engraftment of gene-modified cells
- Expression of WASP
- Platelet count
- Mean platelet volume
- T-cell function
- Antigen-specific responses to vaccinations
- Eczema score
- Autoimmunity phenomena
- Hospitalizations
- Quality of life

Exploratory Efficacy

- Analysis of IgRT
- Antimicrobial treatment
- Platelet activation profile
- Insertion site analysis

6.2.9 Statistical Considerations & Statistical Analysis Plan

See the statistical reviewer's memo for discussion of the statistical analysis plan.

An integrated analysis of efficacy is discussed in section [7.1.4](#).

6.3 Expanded Access Program

The EAP included HE 205030, hematopoietic stem cell GT for the WAS prepared on nonroutine basis; and CUP 206257, CUP for hematopoietic stem cell GT for WAS.

The HE and CUP protocols, which together form the EAP, were based on the design of the TIGET-WAS study (201228) There were no differences in clinical or biological assessments between the HE and CUP protocols.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The following indication is proposed for WASKYRA: "Treatment of patients with WAS aged 6 months and older who have a mutation in the *WAS* gene and for whom no suitable HLA-matched related hematopoietic stem cell donor is available."

7.1.1 Methods of Integration

Patients who received WASKYRA (n=27) treatment from the two clinical studies (TIGET-WAS and OTL-103-4) and the two expanded access studies were integrated for efficacy analyses. One patient in the EAP who underwent mobilization but did not receive RIC and WASKYRA was excluded from the analyses.

Reviewer Comment: *Given the similar protocols across the clinical studies and expanded access populations, it was considered suitable for an integrated interpretation of efficacy analyses.*

7.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics of the 27 patients are shown in Table 6. With the exception of two patients in the EAP, all patients were under 18 years of age at the time of treatment. Median age at treatment was 2.56 years (range: 0.98-35.06).

All patients were symptomatic at the time of enrollment and were considered to have severe WAS characterized by severe clinical phenotype (Zhu clinical score ≥ 3.0), and/or severe genetic mutation, and/or a major deficit in WASP expression. One patient with a Zhu score of 2.0 was identified as having severe WAS due to the presence of a severe *WAS* mutation. The *WAS* gene mutations were Class I in 5 patients and Class II in the other 22 patients.

Expression of WASP in lymphocytes was absent (<5% cells expressing WASP) at baseline in just over half of patients (n=15), reduced in 3 patients, revertant (due to a lymphocyte population expressing normal levels of WASP and representing >5% of total lymphocytes) in 1 patient, and present in 7 patients. Upon reanalysis, four additional patients were reported as having a revertant population of WASP positive lymphocytes.

Table 6: Baseline Characteristics of Efficacy Population

Baseline Characteristics	WASKYRA, N=27
Age on date of gene therapy in years, median (range)	2.562 (0.98, 35.06)
Zhu score at baseline, n (%)	-
2.0	1 (3.7)
3.0	13 (48.1)
4.0	4 (14.8)
5.0A	8 (29.6)
Missing ^a	1 (3.7)
WAS gene mutation at baseline, n (%)	-
Class I	5 (18.5)
Class II	22 (81.5)
WASP expression in lymphocytes at baseline, n (%)	-
Absent (<5% cells expressing WASP)	15 (55.6)
Reduced (>5–<20% cells expressing WASP)	3 (11.1)
Present (>20% cells expressing WASP)	7 (25.9)
Presence of revertant (presence of a subpopulation of lymphocytes expressing normal levels of WASP and representing >5% of lymphocytes) ^b	1 (3.7)
Missing	1 (3.7)

Source: Adapted from BLA125846/0 – Module 2.5, Clinical Overview

^a A baseline Zhu score of 5.0A in one patient was windowed to the treatment visit because it was assessed after the start of mobilization for peripheral blood stem cell collection.

^b Four further patients were reported as having a revertant population of WASP positive lymphocytes, which was detected on reanalysis. Abbreviations: n (%), number of patients with the specified characteristic; N, number of patients in the specified group, or the total sample; WAS, Wiskott-Aldrich syndrome; WASP, Wiskott-Aldrich syndrome protein

7.1.3 Patient Disposition

One adult patient died 4.5 months after GT due to an SAE of neurological decompensation that was considered unrelated to WASKYRA. No patients have been lost to follow-up or have dropped out of the study due to AEs (Table 7). Patients in Study TIGET-WAS and the EAP have completed the study and are now enrolled in a separate long-term follow-up study. Study OTL-103-4 (n=10) is still ongoing.

Follow-up of all 26 surviving patients is ongoing. Median duration of follow-up for the 27 patients in the Efficacy population was 5.67 years (range: 0.37–13.26 years).

Table 7: Patient Disposition

Disposition	WASKYRA
Number (%) of patients in the Integrated Summary of Efficacy population	27 (100)
Number (%) of patients completed 6 months	26 (96.3)
Number (%) of patients completed 1 year	26 (96.3)
Number (%) of patients completed 1.5 years	24 (88.9)
Number (%) of patients completed 2 years	22 (81.5)
Number (%) of patients completed 2.5 years	22 (81.5)
Number (%) of patients completed 3 years	22 (81.5)
Number (%) of patients completed 4 years	21 (77.8)
Number (%) of patients completed 5 years	15 (55.6)

Disposition	WASKYRA
Number (%) of patients completed 8 years	8 (29.6)
Number (%) of patients completed 10 years	5 (18.5)
Number (%) of patients completed 13 years	1 (3.7)
Number (%) of patients ongoing	10 (37.0)
Number (%) of patients withdrawing from the study/program	17 (63.0)
Study withdrawal/completion reason, n (%)	-
Death	1 (3.7)
Study/program closed/terminated	16 (59.3)

Source: Adapted from BLA125846/0 – Module 2.5, Clinical Overview
Abbreviation: n (%), number of patients with the specified characteristic

7.1.4 Analysis of Primary Endpoint(s)

The primary endpoints in the integrated analyses of efficacy are OS, the rate of moderate and severe bleeding events in the first 12 months post-treatment, and the rate of severe infections from 6 to 18 months post-treatment.

Reviewer Comment: *One of the limitations of the clinical data submitted to this BLA was that the endpoints were not pre-specified in the clinical study protocols as the primary efficacy endpoints. However, the endpoints were endorsed by the European Medicines Agency during the 2015 protocol assistance (EMA/H/SA/2996/1/2014/ADT/III), and the choice of endpoints was endorsed during the 2020 European Medicines Agency protocol assistance (EMA/H/SA/2996/2/2020/PA/SME/ADT/III). The FDA had previously recommended that a future clinical study prespecify these endpoints with a defined threshold for meaningful reductions for severe infection and moderate/severe bleeding rates. During the BLA review, the review team exercised regulatory flexibility in review*

7.1.4.1 Overall Survival

Twenty-six patients in the efficacy population were alive at the time of this analysis. One adult patient in the EAP died 4.5 months post-treatment. This patient's death was not considered to be related to WASKYRA by the treating physician or the Applicant; however, relatedness to the conditioning regimen could not be excluded. The proportion of patients surviving at the end of follow-up was 96% (95% CI: 82, 99). The median duration of patient follow-up in all surviving patients was 5.72 years ranging from 1.19 to 13.26 years. Overall survival rates of patients in Studies TIGET-WAS and OTL-103-4 were both 100% at last follow up.

Reviewer Comment: *A systematic literature review² submitted in the BLA reported 1-year OS rate of 92.2% and 5-year OS rate of 74-92% in patients with WAS who received HSCT compared to 1-year and 5-year OS rates of 96% after WASKYRA treatment. In a study of 577 patients with WAS by Vallée et al. 2024, OS of the cohort (censored at HSCT or GT) was 82% (95% CI: 78-87) at 15 years of age and 70% (95% CI: 61-80) at 30 years of age.*

Interpretation of OS data is challenging. The single-arm study design lacks a contemporaneous control group; therefore, direct comparisons to the historical HSCT outcomes could potentially be confounded by differences in patient selection, conditioning regimen, supportive care advances, and treatment era effects. The relatively short median follow-up of 5.7 years, while

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

substantial for a rare disease GT program, may not capture potential late complications or treatment failures that could emerge with longer observation periods. The small sample size (n=27) limits statistical power for detecting rare but SAEs, and the highly selected patient population treated at specialized centers may not reflect outcomes achievable in broader clinical practice. Additionally, the comparison to historical HSCT data may be biased by improvements in supportive care, conditioning regimens, and patient management that have occurred over time. Despite these limitations, the consistent survival benefit observed across different studies (TIGET-WAS: 100%, OTL-103-4: 100%, EAP: 89%), combined with the absence of GVHD and reduced conditioning intensity compared to HSCT, provides compelling evidence that WASKYRA offers a favorable risk-benefit profile with excellent survival outcomes for patients with severe WAS who lack suitable donors or are at high risk for transplant-related complications.

7.1.4.2 Severe Infections

Severe infections, defined as CTCAE Grade 3 or above "Infections and infestations" events, were recorded in the eCRF and analyzed based on specific MedDRA terms. The rate of severe infections was compared between the 12-month period before GT and the 6- to 18-month period after WASKYRA infusion. The first 6 months post-infusion were excluded from this comparison due to the immunosuppressive effects of the conditioning regimen and ongoing immune reconstitution.

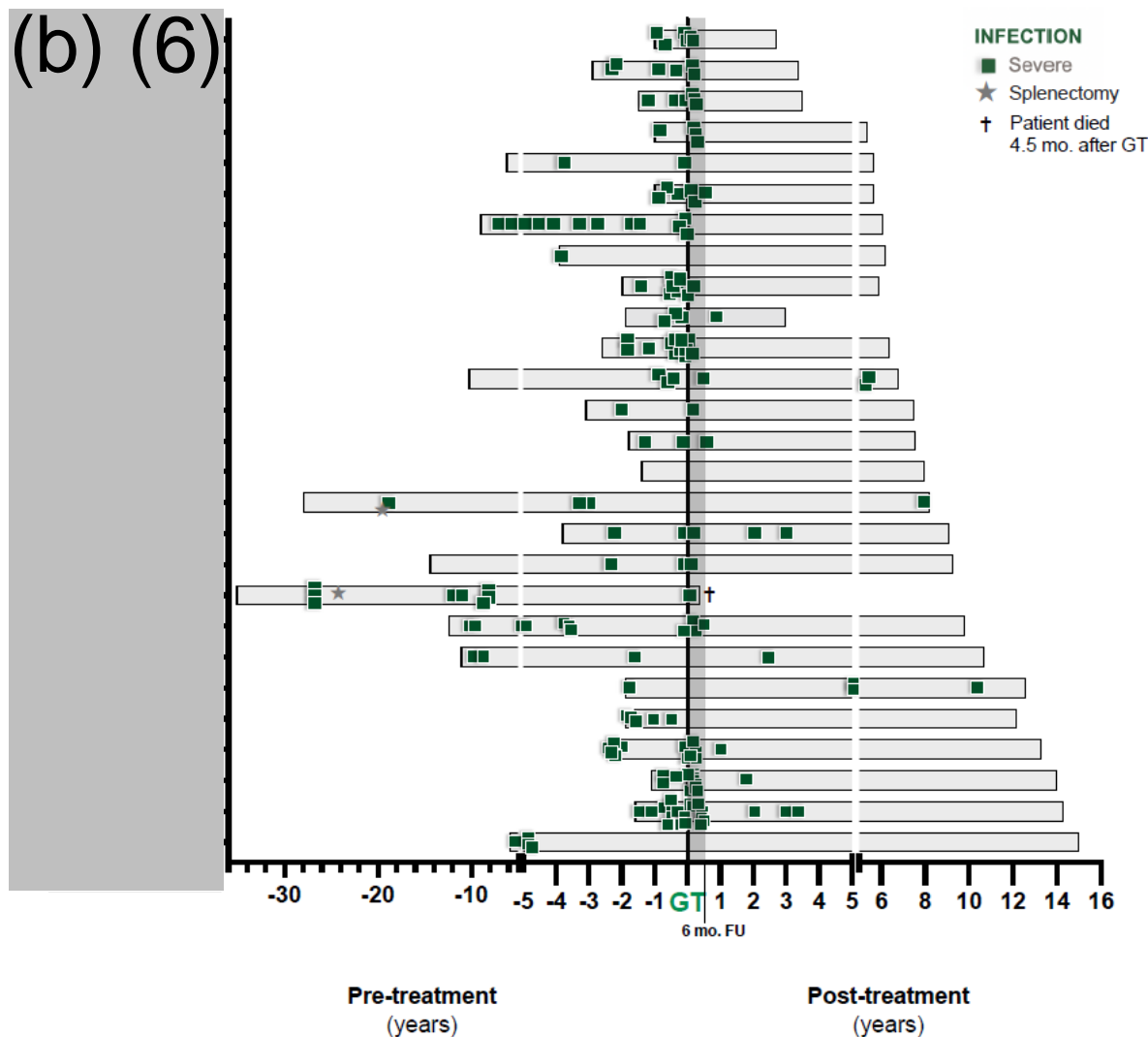
The rate of severe infections decreased from 2.0 (95% CI: 1.50, 2.61) infections per PYO in the 12 months period before treatment to 0.2 (95% CI: 0.04, 0.40) infections per PYO in the 6- to 18-month period post WASKYRA.

Three (11.1%) patients had greater than 5 severe infections each in the 12 months period before GT, whereas 16 patients had 1 to 5 severe infections over the same time period. Nine (34.6%) patients experienced one or more severe infections during the entire follow-up phase following 6 months post-WASKYRA infusion.

There was no meaningful 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 >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. A similar trend of reduction in severe infections was observed in EAP patients ([Figure 4](#)).

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

Figure 4: Severe Infections Over Time in WASKYRA-Treated Patients



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

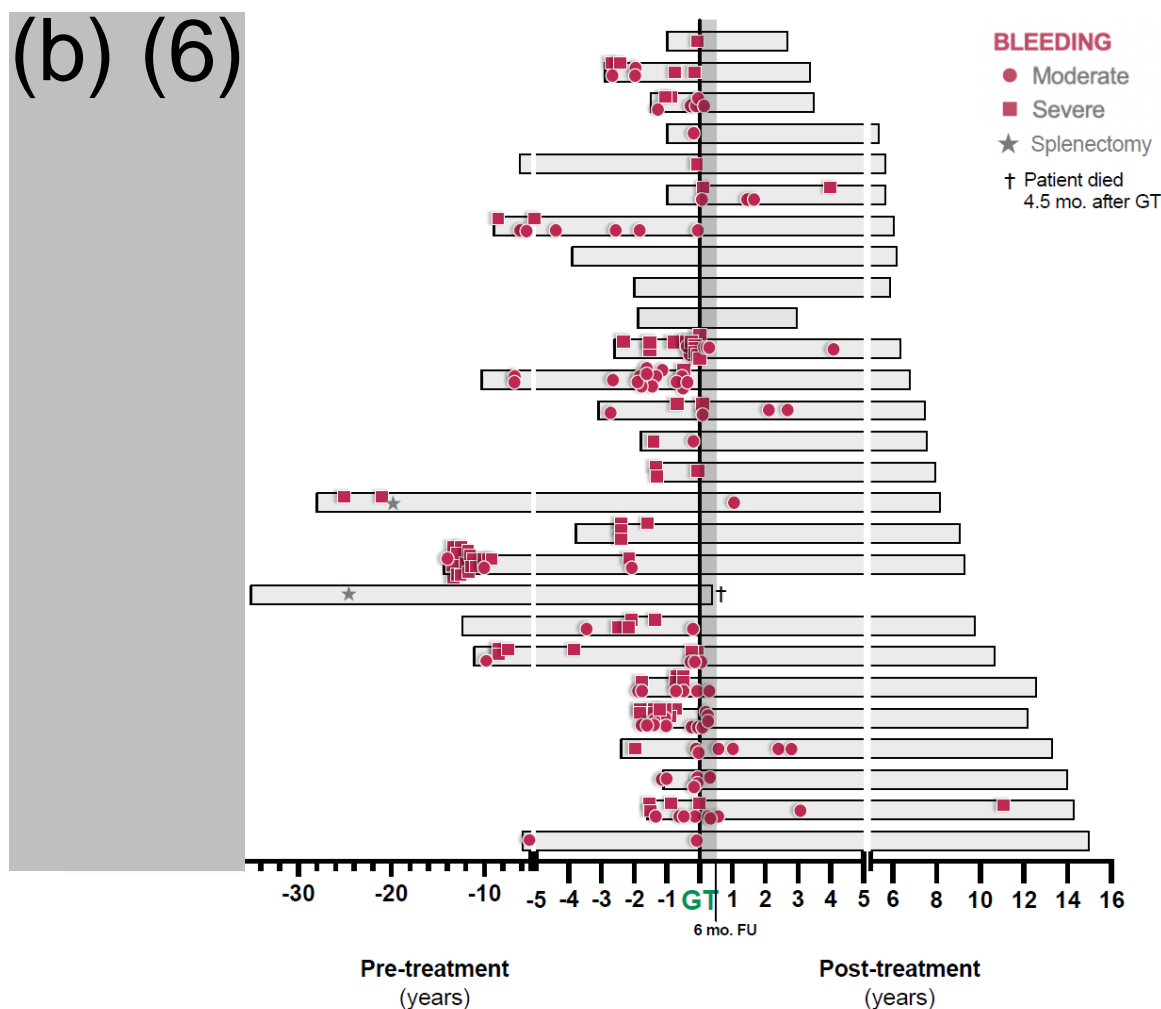
Reviewer Comment: The majority of pre-treatment baseline events were collected retrospectively, and events after screening were collected prospectively per protocol. To minimize underreporting and recall bias during the studies, patients and families were instructed to provide frequent updates between follow-up visits. Discharge letters reminded patients to send copies of local clinical and laboratory reports to the clinical sites. Several contact methods were provided to patients to facilitate communication with the clinical site. Patients were advised to report any signs of infection to local doctors immediately. Local referring doctors were engaged in routine patient management post-treatment. Regular updates between clinical study investigators and local doctors were recorded in clinical notes. Dedicated update calls were organized when needed. This collaborative approach between patients, families, local doctors, and treating physicians ensured accurate event reporting and successful data management. The risk of underreporting of baseline events cannot be ruled out, as most pre-treatment data were collected retrospectively. Of note, underreporting of the events of special interest, would have impacted the interpretation and conclusion of the observed post-treatment improvement in a less favorable result for WASKYRA, since underreporting of baseline events would have

resulted in an underestimation of post-treatment improvement. Furthermore, the reduction of severe infections was supported by immune reconstitution and improvement in cell function and diversity.

7.1.4.3 Moderate and Severe Bleeding Events

Bleeding events were defined from a Customized Query based upon MedDRA Hemorrhage (excluding Laboratory Terms), SMQ (Narrow). The investigator or sub-investigator determined whether events of astringent therapy, disseminated intravascular coagulation, hyperfibrinolysis, and immune thrombocytopenia were bleeds or not. Five events were excluded from the calculation of the numbers and annualized rates of bleeding events presented in this section (one event of immune thrombocytopenia that occurred in the 12 months prior to GT and four that occurred post GT: three events of immune thrombocytopenia and one event of disseminated intravascular coagulation). Moderate and severe bleeding events in individual patients are shown in [Figure 5](#).

Figure 5: Moderate and Severe Bleeding Events Over Time



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

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 GT to 0.8 (95% CI: 0.49, 1.22) events per PYO in the 12 months following WASKYRA, and 0.03 (95% CI: 0.003, 0.099) events per PYO in the >4-year period.

The most frequent moderate and severe bleeding event in the 12 months before WASKYRA was petechiae; nine moderate events reported in five (18.5%) patients and three severe events reported in two (7.4%) patients. The most frequent event in the 12 months post-WASKYRA infusion was also petechiae, with 14 moderate events reported in 7 (25.9%) patients and 1 severe event in 1 (3.7%) patient. The only other moderate or severe bleeding event reported in that period in more than one patient was epistaxis, with nine events of moderate severity reported in five (18.5%) patients. Bleeding events most commonly occurred in skin and subcutaneous tissue disorders (43% in the 12 months before GT versus 45.4% post), followed by the gastrointestinal disorders (29.6% versus 26.8%).

Severe Bleeding

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 GT to 0.08 (95% CI: 0.01-0.27) events per PYO in the 12 months following WASKYRA, 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 GT to 0.7 (95% CI: 0.43-1.13) events per PYO in the 12 months following WASKYRA. At >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 WASKYRA infusion. No Grade 4 severe bleeding events were reported up to the data cut-off of both the TIGET-WAS and OTL-103-4 studies and the EAP. The remaining two severe bleeding events occurred 3 to 4, and >4 years post-treatment, respectively.

Moderate Bleeding

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

Reviewer Comment: *The potential impact of recall and documentation bias with retrospective baseline data are discussed in [Section 7.1.4.2](#). Despite the limitations of single-arm design and small sample size, the reduction in the bleeding rate is clinically meaningful given the life-threatening nature of bleeding events in WAS. Benefits sustained over >4 years of follow-up. The functional improvement was accompanied by platelet count recovery and WASP expression (discussed in [Section 7.1.5](#)). The sustained benefit despite incomplete platelet normalization could be suggestive of effects on improved platelet function.*

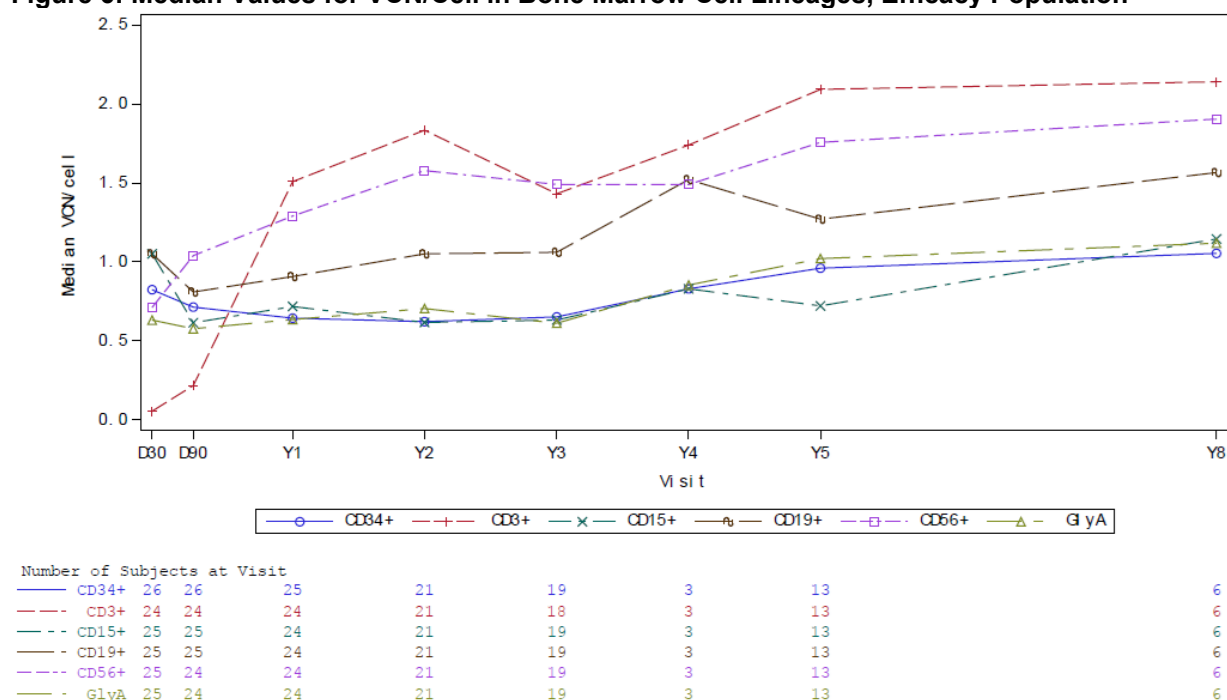
7.1.5 Analysis of Secondary Endpoint(s)

The key secondary endpoints in the integrated efficacy analysis were as follows:

7.1.5.1 Engraftment of Genetically Corrected Hematopoietic Stem Cells in PB and BM Over Time

Adequate engraftment is defined as either ≥ 0.04 VCN/cell (equivalent to 4% gene-marked cells assuming a VCN of 1) in BM CD34+ cells, or ≥ 0.1 VCN/cell (equivalent to 10% gene-marked cells assuming a VCN of 1) in PB CD3+ cells. The median VCN/cell in BM and PB cell lineages are presented in [Figure 6](#) and [Figure 7](#), respectively. Adequate engraftment of gene-modified cells was observed in all patients, with a median time to engraftment of 32 days. This engraftment was multilineage, affecting both BM and PB cell populations, and was maintained in evaluable patients for up to 8 years post-treatment.

Figure 6: Median Values for VCN/Cell in Bone Marrow Cell Lineages, Efficacy Population

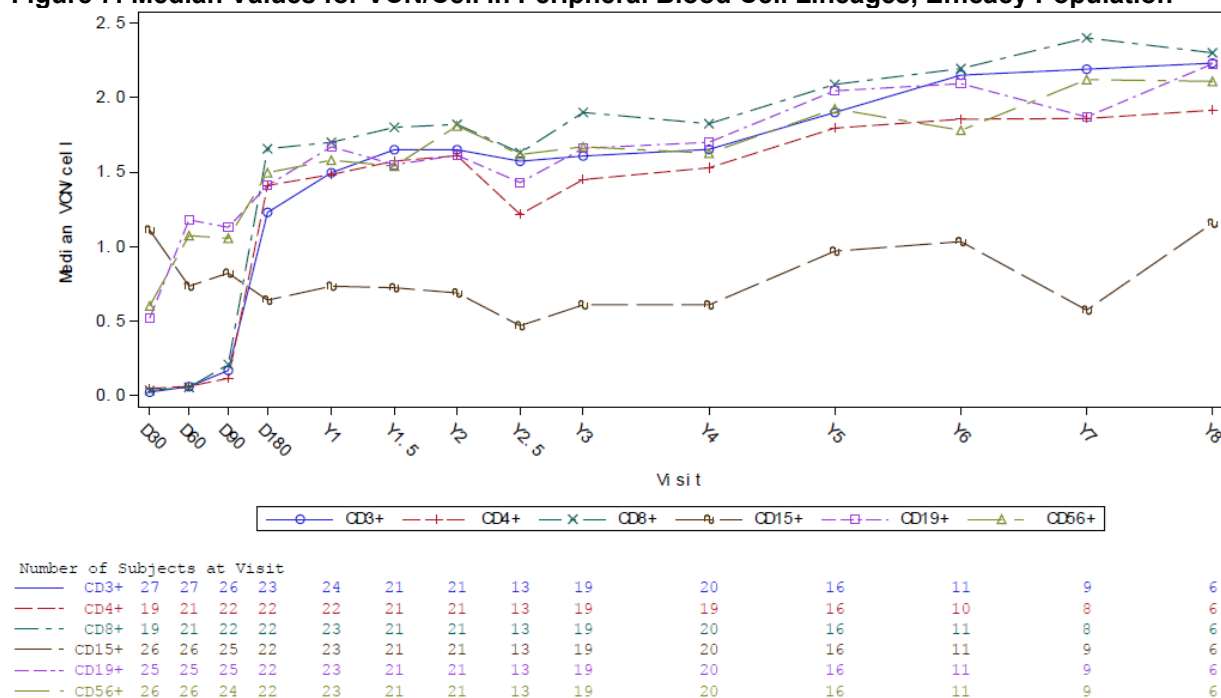


Source: Summary of Clinical Efficacy submitted by the Applicant

Results based on fewer than two patients were omitted.

Abbreviations: D, Day; CD, cluster of differentiation; GlyA, glycophorin A; VCN, vector copy number; Y, Year

Figure 7: Median Values for VCN/Cell in Peripheral Blood Cell Lineages, Efficacy Population



Source: Summary of Clinical Efficacy submitted by the Applicant

Results based on fewer than two patients were omitted.

Abbreviations, D, Day; CD, cluster of differentiation; GlyA, glycophorin A; VCN, vector copy number; Y, Year

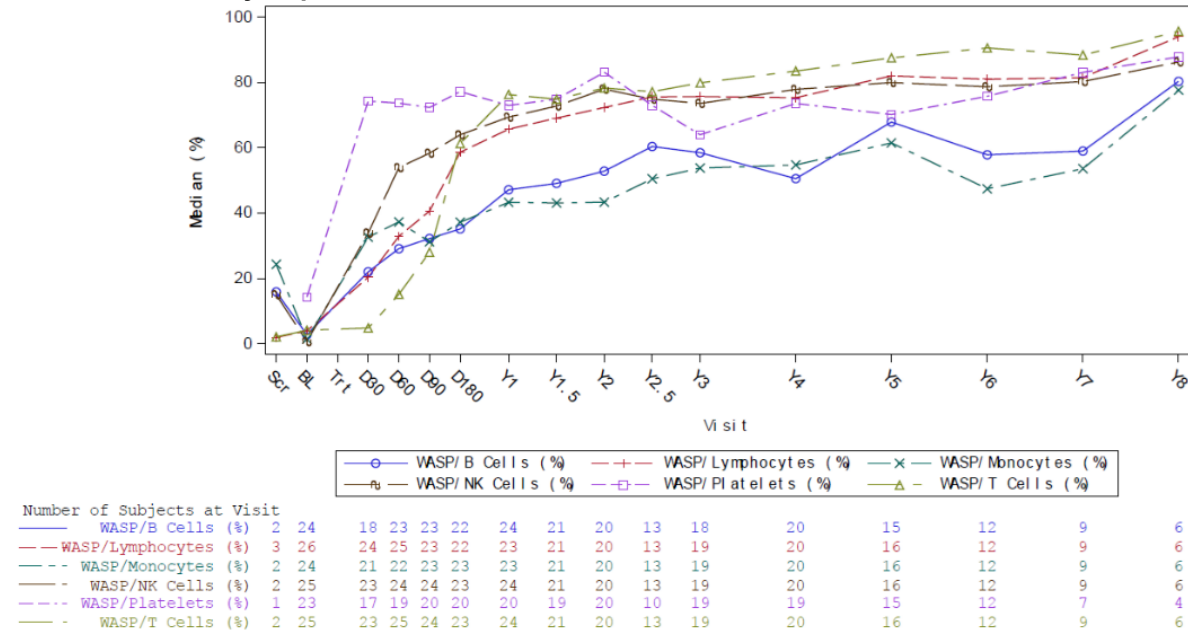
The data demonstrate sustained engraftment of genetically corrected cells in all patients treated with WASKYRA. All patients achieved hematological reconstitution, with 92.6% (25/27) reaching an absolute neutrophil count >500 cells/ μ L by Day 60 post-treatment. The median percentage of gene-modified cells in BM was around 50% at Years 1 and 2, indicating stable long-term engraftment.

Overall, these results show successful and durable genetic correction across various hematopoietic lineages following WASKYRA treatment.

7.1.5.2 WASP Expression

WAS protein expression increased in all PB cell types (platelets, lymphocytes, B-cells, T-cells, natural killer cells, and monocytes) after WASKYRA infusion, as shown in [Figure 8](#) below. In platelets, median WASP expression rose from 14.30% at baseline to 74.30% at Day 30, reaching 77.20% by Day 180 and remaining stable thereafter. Lymphocyte WASP expression increased more gradually, from 3.92% at baseline to 58.65% at Day 180, and continued to rise, exceeding 70% from Year 2 onwards. T-cells showed a delayed increase in WASP expression, occurring mainly between Day 60 and Day 180, due to their complex maturation process in the thymus. WASP expression in T-cells continued to increase gradually over time, consistent with a selective advantage for WASP-expressing cells in the lymphoid compartment. Overall, the median percentage of PB cells expressing WASP remained relatively stable from Day 180 to the final analyzed timepoint at Year 8, demonstrating sustained correction of the underlying genetic defect, as shown in Table 8 below.

Figure 8: Median Values of Peripheral Blood Cells Expressing WASP Assessed by Flow Cytometry Over Time, Efficacy Population



Source: Applicant's Summary of Clinical Efficacy

Note: Transduced cells infusion (gene therapy) was performed at the Treatment Visit (Trt).

Results based on fewer than two patients are omitted.

Patients enrolled at the Children's Healthcare of Atlanta site do not have WASP expression assessed in platelets.

Abbreviations: BL, Baseline; D, Day; NK, natural killer; Scr, Screening; Trt, Treatment (WASKYRA); WASP, Wiskott-Aldrich syndrome protein; Y, Year

Table 8: Statistics of Cells Expressing WASP, Efficacy Population

% of cells expressing WASP in PB	Baseline	Change from baseline														
	Median (Min, Max) [n]	Day 30 Median (Min, Max) [n]	Day 60 Median (Min, Max) [n]	Day 90 Median (Min, Max) [n]	Day 180 Median (Min, Max) [n]	Year 1 Median (Min, Max) [n]	Year 1.5 Median (Min, Max) [n]	Year 2 Median (Min, Max) [n]	Year 2.5 Median (Min, Max) [n]	Year 3 Median (Min, Max) [n]	Year 4 Median (Min, Max) [n]	Year 5 Median (Min, Max) [n]	Year 6 Median (Min, Max) [n]	Year 7 Median (Min, Max) [n]	Year 8 Median (Min, Max) [n]	
Platelets	14.30 (3.2, 35.8) [23]	58.10 (1.9, 95.5) [15]	57.65 (10.4, 87.3) [16]	56.30 (32.8, 76.8) [17]	60.50 (39.8, 91.9) [17]	52.40 (34.4, 84.4) [17]	64.50 (33.0, 82.6) [17]	69.30 (10.9, 84.9) [17]	57.60 (22.0, 79.8) [8]	50.55 (13.9, 76.1) [16]	58.65 (28.5, 77.8) [16]	64.10 (29.0, 80.7) [14]	64.00 (0.3, 74.3) [11]	68.70 (49.9, 81.7) [6]	71.05 (53.5, 95.5) [4]	
Lymphocytes	3.920 (0.20, 85.10) [26]	11.400 (-28.10, 50.80) [24]	19.800 (-30.00, 48.40) [25]	24.000 (-23.10, 73.50) [23]	50.800 (-17.20, 65.60) [22]	57.500 (-18.20, 91.16) [23]	62.340 (-10.00, 84.60) [21]	63.650 (-16.50, 94.60) [20]	71.600 (-8.90, 81.34) [13]	70.460 (2.40, 81.60) [19]	69.980 (-9.70, 89.90) [20]	72.880 (-3.90, 90.20) [16]	73.650 (-1.90, 86.30) [12]	77.000 (15.30, 91.80) [9]	72.580 (60.90, 94.50) [6]	
B-cells	2.750 (0.10, 45.20) [24]	20.100 (-24.00, 36.00) [17]	19.900 (-0.20, 55.50) [21]	28.600 (-22.80, 84.10) [20]	33.800 (-18.00, 66.60) [19]	35.800 (-25.50, 82.70) [21]	41.360 (-14.10, 85.10) [18]	50.300 (-14.20, 92.90) [17]	54.050 (-32.40, 66.30) [10]	47.500 (-24.00, 90.40) [15]	40.820 (-9.50, 70.70) [17]	58.450 (17.10, 69.52) [12]	52.500 (-17.60, 64.60) [10]	39.200 (-6.50, 60.80) [7]	52.150 (4.10, 72.50) [4]	
T-cells	4.100 (0.00, 85.20) [25]	0.500 (-28.20, 47.10) [23]	3.895 (-30.50, 54.70) [24]	12.295 (-22.20, 61.80) [22]	52.600 (-24.90, 78.10) [21]	56.400 (-3.50, 86.20) [22]	68.300 (-7.80, 87.70) [19]	64.650 (-9.10, 96.80) [18]	73.600 (-5.90, 89.80) [11]	70.200 (6.60, 92.40) [17]	72.550 (-6.00, 98.30) [18]	68.600 (-0.40, 92.30) [14]	78.050 (27.90, 90.10) [10]	84.400 (44.80, 93.10) [7]	77.750 (64.00, 97.30) [4]	
NK cells	0.600 (0.00, 80.62) [25]	25.000 (-24.40, 65.40) [22]	42.300 (-32.82, 77.50) [23]	50.050 (-35.40, 81.40) [22]	58.300 (-20.92, 86.10) [21]	59.215 (-16.90, 83.00) [22]	66.100 (2.28, 80.90) [19]	68.250 (-1.02, 92.60) [18]	54.900 (-22.60, 86.80) [11]	67.300 (-6.80, 85.30) [17]	73.115 (-5.10, 89.70) [18]	69.515 (-19.70, 89.20) [14]	71.350 (-14.10, 87.60) [10]	75.500 (-2.80, 94.00) [7]	59.100 (43.50, 90.90) [4]	
Monocytes	1.400 (0.00, 98.20) [24]	23.160 (-14.40, 77.40) [20]	27.500 (-44.40, 56.90) [21]	27.950 (-68.60, 91.60) [22]	35.220 (-77.10, 93.30) [21]	36.000 (-79.50, 94.60) [20]	44.000 (-63.80, 92.70) [18]	34.500 (-7.80, 94.20) [17]	47.020 (-28.80, 63.80) [11]	40.400 (-8.50, 95.60) [16]	37.500 (-7.30, 96.70) [17]	34.700 (-1.20, 83.10) [13]	40.400 (-73.30, 73.90) [9]	40.700 (-65.50, 98.50) [6]	68.300 (34.80, 81.50) [3]	

Source: Applicant's Summary of Clinical Efficacy

Note: WASP expression was assessed by flow cytometry.

If there is more than one value within an assessment window, the earliest available measurement for that visit has been used in the summary.

Patients enrolled at the Children's Healthcare of Atlanta site do not have WASP expression assessed in platelets.

Abbreviations: n, number of patients with the specified characteristic; WASP, Wiskott-Aldrich syndrome protein

Reviewer Comment: *As noted previously, one patient in Study TIGET-WAS had a revertant population of WASP positive lymphocytes at baseline, and four patients in the EAP program had a revertant population of WASP positive lymphocytes at baseline upon reanalysis. High incidence of somatic revertant mosaicism has been reported in patients with WAS. Revertant population of WASP positive cells are due to a wide range of changes including silent nucleotide substitutions, compensatory or second-site mutations of WAS restoring the reading frame, or true genetic reversions to the wild-type sequence. The flow cytometry-based assessment relies (b) (4) detection and may not capture all functional aspects of WASP protein activity. The impact of the revertant cell populations on functional outcome measure is unclear. In addition, the mixed chimerism (~50% genetically corrected cells) underlying these expression levels raises questions about whether incomplete correction might limit therapeutic potential for some disease manifestations. Despite these limitations, multilineage engraftment observed in treated patients underscores the functional improvement observed in treated patients. The strong temporal correlation between WASP expression recovery and clinical improvement, combined with the biological rationale and sustained durability over extended follow-up, provides compelling evidence that WASKYRA achieves clinically meaningful restoration of WASP function that translates into substantial therapeutic benefit for patients with WAS.*

7.1.5.3 T-Cell Function

T-cell function, as represented by counts per minute and stimulation index, improved following treatment with WASKYRA, as shown in Table 9 below. At baseline, all patients showed reduced proliferative responses to CD3 stimulation. After treatment, in vitro T-cell proliferation increased over time when stimulated with immobilized CD3 (CD3i) antibodies. The most pronounced improvement was observed with the highest concentration of CD3i (1 µg/mL), where the median stimulation index increased from 30.20 at baseline to 153.55 at Year 2, and further to 210.70 at Year 8. Improvements were also seen at lower CD3i concentrations, though these were smaller and occurred later. By Year 2 post-treatment, T-cell proliferative responses were within the normal range, demonstrating that T-cell function had normalized following WASKYRA infusion. This improvement in T-cell function was maintained over time, indicating a sustained restoration of this critical aspect of immune function.

Table 9: Statistics of T-Cell Function, Efficacy Population

Anti-CD3i Concentration	Baseline	T-cell proliferative response to stimulation, change from baseline								
	Median (min, max)	Day 180 Median (min, max)	Year 1 Median (min, max)	Year 2 Median (min, max)	Year 3 Median (min, max)	Year 4 Median (min, max)	Year 5 Median (min, max)	Year 6 Median (min, max)	Year 7 Median (min, max)	Year 8 Median (min, max)
Lymphocyte proliferative response (CPM)										
n	26	21	22	20	18	20	14	11	7	5
0.01 µg/mL	303.5 (52, 5190)	121.0 (-860, 2414)	147.0 (-1145, 14,908)	464.5 (-318, 32,181)	804.0 (-620, 16,150)	978.5 (-1029, 30,655)	542.0 (-800, 15,829)	738.0 (-878, 8412)	211.0 (-780, 3174)	2238.0 (-204, 3108)
0.1 µg/mL	1292.5 (76, 27,194)	967.0 (-14,596, 11,076)	3423.0 (-14,788, 41,633)	12,490.5 (-10,328, 80,079)	15,267.5 (-1268, 125,664)	17,096.0 (-14122, 71,183)	8759.0 (-9835, 46,840)	18,093.0 (-7554, 49,886)	1392.0 (325, 33,866)	35,790.0 (-4824, 117,556)
1 µg/mL	5800.5 (125, 49,038)	11,566.0 (-29,635, 90,207)	22,565.5 (-28,924, 236,325)	41,870.5 (-2689, 108,374)	42,773.5 (-3331, 368,156)	50,837.5 (-16,813, 185,891)	52,522.0 (5576, 168,398)	42,416.0 (719, 164,972)	13,203.0 (4235, 131,962)	66,532.0 (8891, 225,120)
Lymphocyte proliferative response (SI)										
n	26	21	22	20	18	20	14	11	7	5
0.01 µg/mL	1.20 (0.2, 55.8)	-0.10 (-7.9, 47.4)	0.40 (-3.6, 35.9)	0.75 (-1.2, 17.4)	1.20 (-2.4, 22.0)	0.80 (-0.5, 48.7)	0.45 (-6.8, 18.5)	1.10 (-7.4, 44.9)	0.40 (-8.7, 6.6)	1.80 (-0.6, 7.5)
0.1 µg/mL	4.70 (0.5, 292.4)	2.50 (-36.2, 100.4)	11.45 (-45.4, 98.8)	36.55 (-51.9, 227.1)	60.55 (-21.1, 141.2)	15.40 (-9.8, 132.8)	24.10 (-55.4, 134.5)	34.20 (-16.1, 246.0)	11.50 (-9.4, 70.8)	31.20 (5.1, 310.9)
1 µg/mL	30.20 (0.5, 527.3)	24.10 (-75.0, 220.7)	85.20 (-49.8, 449.5)	119.75 (-67.9, 366.5)	153.20 (-40.4, 275.4)	94.25 (-7.6, 337.6)	118.40 (7.1, 883.0)	127.00 (66.3, 438.8)	49.80 (32.1, 251.0)	145.20 (57.1, 427.3)

Source: Applicant's Summary of Clinical Efficacy

Note: If there was more than one value within an assessment window, the earliest available measurement for that visit was used in the summary.

Lymphocyte proliferation was assessed using different units (%) at the Children's Healthcare of Atlanta site to the SR-TIGET site. Therefore, lymphocyte proliferation data for the patient at the CHO site is not summarized in this output but can be found in the supporting listing.

Abbreviations: max, maximum; min, minimum; n, number of patients with the specified characteristic

7.5.1.4 Platelet Count

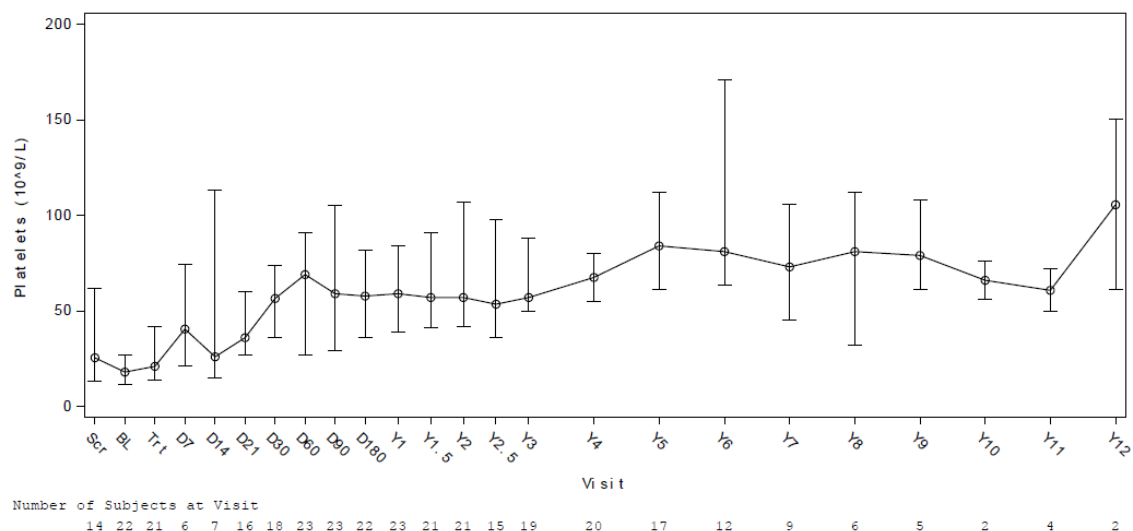
All patients with WAS had thrombocytopenia at baseline, and 23 out of 27 were receiving platelet infusions at the time of treatment. Platelet counts and MPV were measured at different points post-treatment and compared with baseline values, when available. Some platelet count values were excluded because patients were receiving prophylactic platelet transfusions or treatment with off-label thrombopoietin (TPO) agonists at the time of assessment. Similarly, some MPV values were not available, either because patients were receiving platelet transfusions and the MPV was therefore excluded from the analysis, or because the MPV values could not be calculated by the automated blood analyzer due to the low platelet count and small platelet size.

Following WASKYRA infusion, platelet counts increased and remained stable over time ([Figure 9](#)). Median platelet count rose from $18.00 \times 10^9/L$ at baseline to $59.00 \times 10^9/L$ at Year 1, and further to $84.00 \times 10^9/L$ at Year 5. By Year 2, no patients had platelet counts below $20 \times 10^9/L$, and most maintained counts between 50 and $100 \times 10^9/L$ throughout follow-up. Three of the 24 evaluable patients achieved normal platelet counts ($\geq 150 \times 10^9/L$) at Year 1. The increase in platelet counts sustained in evaluable patients up to Year 13.

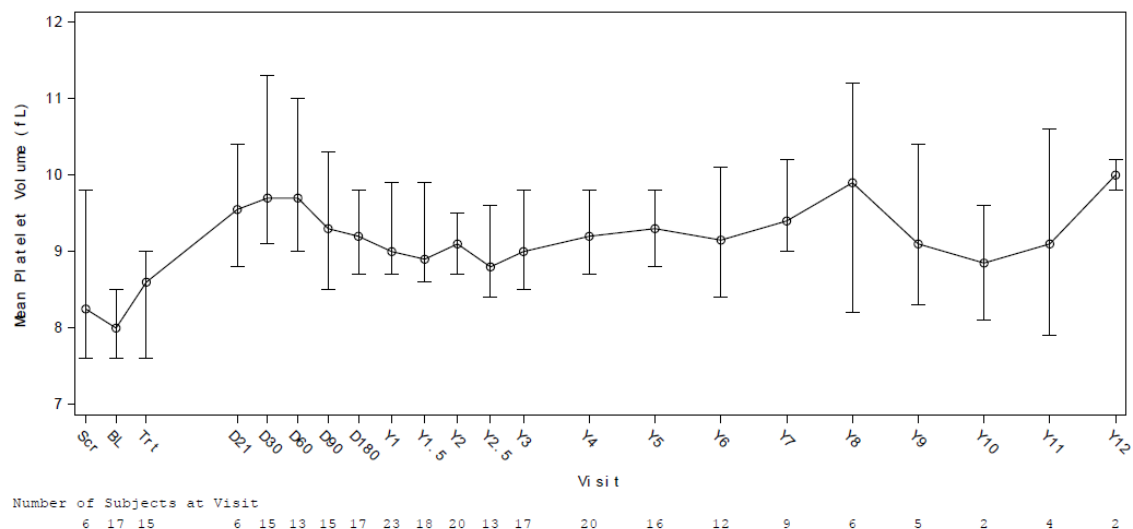
Median (range) MPV increased from 8.0 (6.8-10.0) fL at baseline to 9.0 (7.5-12.9) fL at Year 1 and remained at a sustained increase at all subsequent timepoints, including past Year 9. An exploratory analysis of platelet activation profile in WASKYRA patients indicated a restoration of platelet function after WASKYRA infusion (Sereni et al. 2019).

Figure 9: Median (95% Confidence Interval) Values of Mean Platelet Count and Platelet Volume Over Time, Efficacy Population

Platelet count



Mean platelet volume



Source: Applicant's Clinical Summary of Efficacy

Note: Transduced cells infusion (gene therapy) was performed at the Treatment Visit (Trt).

Platelet samples taken within 7 days of a platelet transfusion, 25 days of romiplostim, or 14 days of eltrombopag were excluded from the calculation of data displayed in this output.

MPV samples taken within 7 days of a platelet transfusion were excluded from the calculation of data displayed in this output.

Results based on fewer than two patients were omitted.

Abbreviations: BL, Baseline; CI, confidence interval; D, day; MPV, mean platelet volume; Scr, Screening; Trt, Treatment (WASKYRA); Y, Year

7.5.1.5 Platelet Infusions and Thrombopoietin Receptor Agonists

Following WASKYRA treatment, there was reduced need for platelet infusions and TPO receptor agonists. The annualized rate of platelet infusions decreased from 10.84 per PYO pre-treatment to 1.69 per PYO in the 6 to 12-month period post-treatment, and further to 0.18 per PYO in the entire >6 months post-treatment period. All 23 evaluable patients achieved

cessation of sustained platelet infusions within 9 months post-treatment, with a median time to platelet transfusion independence of 49 days (range: 9-261 days).

Additionally, the use of off-label TPO receptor agonists (romiplostim and eltrombopag), which were employed in seven patients pre-treatment to manage severe thrombocytopenia, was successfully discontinued in all patients by Year 2 post-treatment, with only one patient requiring brief TPO agonist therapy for suspected immune thrombocytopenia in the early post-treatment period.

Reviewer Comment: *The median time to transfusion independence of 49 days post-treatment may not reflect treatment effect but rather that patients were able to sustain longer periods without need for transfusions. Chronic platelet transfusion dependency in patients with WAS carries significant risks including alloimmunization, transfusion reactions, iron overload, and infectious disease transmission, while also requiring frequent hospital visits and limiting normal activities of daily living. Despite limitations, the sustained independence from both platelet transfusions and TPO agonists over years of follow-up, combined with the observed reduction in bleeding events, validates the clinical meaningfulness of these hematological improvements.*

7.1.5.6 Autoimmunity

Autoimmunity generally improved following WASKYRA treatment. Eleven patients had clinical manifestations of autoimmunity before GT, most of which resolved during pre-treatment or within the first year post-treatment. Post-treatment autoimmune events were generally transient and occurred mainly in the first 6 months, including four cases of immune thrombocytopenia and one case of autoimmune neutropenia. Later events were rare and mostly mild. The number of positive autoantibody tests decreased from 52 at baseline to 34 at Year 1, and remained at 20 or fewer from Year 3 onwards. The most common autoimmunity-related AEs were the presence of anti-platelet and antineutrophil cytoplasmic antibodies, which often did not correlate with clinical manifestations. Overall, the data suggest that WASKYRA treatment led to a reduction in both clinical and laboratory markers of autoimmunity in most patients.

7.1.5.7 Eczema

WASKYRA treatment demonstrated a beneficial effect on eczema in patients with WAS. At baseline, 23 out of 27 patients had eczema, with 6 cases classified as moderate and three as severe. Following treatment, there was improvement in eczema severity. By Year 1, no patients had moderate or severe eczema. At Year 2, 19 out of 21 evaluable patients (90.5%) were completely free of eczema, with the remaining 2 having only transient symptoms. The improvement continued over time, with no patients experiencing eczema from Year 6 onwards.

7.1.6 Other Endpoints

Hospitalization

Following treatment with WASKYRA, there was a reduction in hospitalization rates for patients with WAS. The annualized rate of hospitalizations, excluding those related to the WASKYRA treatment itself, decreased from 2.9 hospitalizations per PYO in the 12 months before GT to 0.5 hospitalizations per PYO in the 6 to 12-month period post-treatment. This rate further declined to 0.09 hospitalizations per PYO in the period beyond 4 years post-treatment. Notably, hospitalizations specifically for bleeding and severe infections showed an even more dramatic decrease, falling from 1.9 hospitalizations per PYO pre-treatment to 0.08 hospitalizations per

PYO in the period more than 6 months post-WASKYRA. These results demonstrate a substantial reduction in the need for hospital care, indicating improved overall health and management of disease-related complications following WASKYRA therapy.

IgRT Replacement Therapy

Immunoglobulin replacement therapy requirements decreased significantly following WASKYRA treatment. While most patients (85.2%-96.3%) received IgRT in the pre-treatment and early post-treatment phases, the number of patients requiring IgRT dropped substantially over time. By the 2 to 3-year post-treatment period, only 13.6% of patients still needed IgRT. Cessation of sustained IgRT, defined as a 3-month IgRT-free period, was achieved in 23 out of 25 patients (92.0%) who received IgRT post-WASKYRA. The median time to cessation was 313 days (range: 91-1,843 days). By 12 months post-treatment, 56% of patients had discontinued IgRT.

Antimicrobial Therapy

Following WASKYRA treatment, there was a reduction in the need for sustained antimicrobial therapy among patients with WAS. While all patients received antimicrobial medication during the on-treatment phase and the first 6 months post-treatment, the number of patients requiring such treatment decreased over time. By the 2 to 3-year post-treatment period, only 77.3% of patients were receiving antimicrobials, further decreasing to 62.5% in the >8-year follow-up period. Notably, 23 out of 27 patients (85.2%) achieved cessation of sustained antimicrobial treatment, defined as a 3-month period without such therapy. The median time to cessation was 391 days (range: 22-2,534 days). By 12 months post-WASKYRA, 30% of patients had discontinued sustained antimicrobial treatment.

Social Life

WASKYRA treatment led to improvements in the social lives of patients with WAS. At baseline, 55.6% of patients were living in a protected environment; only 36.4% were attending kindergarten/school, and just 4.3% were practicing sports. Following treatment, these metrics improved dramatically. By Year 2, the number of patients living in a protected environment decreased to 27.3%, and from Year 3 onwards, no patients required such protection. School attendance increased to 52.4% at Year 2 and remained high (at least 83%) from Year 4 onwards. Sports participation also increased, with at least 50% of patients engaging in sports from Year 4 onwards. It's worth noting that age and the COVID-19 pandemic may have influenced some of these results, particularly for younger patients and those assessed during lockdowns.

7.1.7 Subpopulations

7.1.7.1 Age at Treatment

In this integrated study, 18 patients were <5 years old and 9 patients were ≥5 years old at the time of GT, with comparable OS achieved in both groups (100% in younger patients, 89% in older patients, with the single death being unrelated to GT). Notably, the engraftment success rate was universal (100%) regardless of age, with similar kinetics for achieving adequate gene-corrected cell engraftment (median 32 days in both groups). WASP expression recovery followed comparable patterns between age groups, with both achieving >60% WASP-positive platelets and >70% WASP-positive lymphocytes by Year 1 to 2. T-cell function restoration was

similarly across ages, with both groups achieving normalized proliferative responses within the first year post-treatment.

In the WASKYRA clinical development program, older patients demonstrated slightly better baseline platelet counts and had no severe bleeding events post-treatment, while younger patients experienced a few severe bleeding episodes but showed more dramatic improvements from their lower baseline values. Older patients (≥ 5 years) had lower rates of severe infections than younger patients in the 12 months period before GT and early post-treatment periods. Beyond the 6-month post-treatment period, the rate of severe infections decreased markedly in both age groups (< 5 years or ≥ 5 years). In patients < 5 years, the rate of infections decreased from 2.50 infections per PYO in the 12 months period before GT to 0.13 infections per PYO beyond 6 months of follow-up. In patients ≥ 5 years, the rate of infections was 1.0 infection per PYO in the 12 months period before GT, and no severe infections were experienced in this age group beyond the 6-months post-treatment period, other than a single infection in the 2 to 3-year period.

Reviewer Comment: *The age-independent efficacy of WASKYRA represents a potential clinical advantage over HSCT, where age > 5 years is associated with substantially worse outcomes (5-year survival $\sim 75\%$ versus $\sim 90\%$ for younger patients). The sustained clinical benefits observed in older patients suggest that GT may be particularly valuable for patients who have aged out of optimal transplant candidacy or lack suitable donors.*

7.1.7.2 Cellular Source

The analysis by cellular source examined outcomes based on whether hematopoietic stem cells were harvested from BM ($n=5$), mPB ($n=21$), or both sources ($n=1$). Universal engraftment success (100%) was achieved regardless of cellular source, though notable differences emerged in baseline disease characteristics and early post-treatment patterns. Bone marrow patients appeared to represent a more severely affected population, with higher pre-treatment bleeding rates (4.2 versus 1.5 events per person-year) and severe infection rates (3.2 versus 1.8 per person-year). The most striking difference occurred in the immediate post-treatment period, where BM patients experienced a dramatic spike in severe infections during the first 6 months (7.6 per person-year) compared to mPB patients (2.2 per person-year).

Despite these early differences, long-term outcomes were similar between cellular sources. Both groups achieved sustained engraftment, comparable WASP expression recovery, and similar infection rates (< 0.2 per person-year) beyond 6 months. Platelet count recovery consistently favored mPB patients throughout follow-up (median $> 65 \times 10^9/L$ versus $< 80 \times 10^9/L$ for BM), aligning with known advantages of mPB grafts in transplant settings. Vector copy numbers and WASP expression levels converged between groups by Years 1 to 4, indicating that cellular source does not significantly impact long-term gene correction magnitude or durability.

7.1.7.3 Drug Product Formulation (Fresh vs Cryopreserved)

Seventeen patients (63%) received the fresh formulation (used in the TIGET-WAS and EAP studies), while 10 patients (37%) received the cryopreserved formulation (used in the OTL-103-4 study). Both formulations achieved universal engraftment success (100%) with similar kinetics and durability of gene-corrected cell engraftment over time. The key efficacy parameters showed no meaningful differences between formulations: WASP expression recovery in both platelets and lymphocytes followed comparable patterns and reached similar peak levels, T-cell

function restoration (measured by lymphocyte proliferation assays) achieved equivalent normalization, and VCNs in both BM CD34+ cells and PB CD3+ cells were sustained at similar levels throughout follow-up. Platelet count recovery and MPV improvements were also comparable between the two formulations, indicating that the cryopreservation process does not compromise the therapeutic potential of the genetically corrected cells.

Reviewer Comment: *The analysis by drug product formulation demonstrates that both fresh and cryopreserved formulations of WASKYRA achieve comparable clinical efficacy, supporting the transition to the cryopreserved formulation for commercial use.*

7.1.7.4 Disease Severity and Genetic Factors

Analyses by baseline Zhu score, WAS gene mutation class, and baseline WASP expression levels revealed consistent therapeutic benefit across the spectrum of disease severity and genetic backgrounds. Patients with Zhu scores ranging from 2.0 to 5.0A all achieved excellent outcomes, with no correlation between baseline disease severity and treatment response. Similarly, both Class I (n=5) and Class II (n=22) WAS mutations showed comparable engraftment success and clinical improvement, though Class II mutations (associated with complete WASP loss) showed slightly better recovery patterns. The analysis by baseline WASP expression compared patients with absent WASP expression (<5%, n=15) to those with detectable levels (n=11, including revertants). Both groups achieved similar final outcomes.

7.1.8 Persistence of Efficacy

Sustained clinical improvements maintained over extended follow-up periods ranging up to 13 years.

7.1.9 Product-Product Interactions

Although concomitant medications were documented for all patients, no product-product interactions were expected or observed during the course of the clinical studies.

7.1.10 Additional Efficacy Issues/Analyses

None.

7.1.11 Efficacy Conclusions

Across 27 patients treated in 2 clinical studies and an EAP, with follow-up extending up to 13.26 years, WASKYRA achieved universal engraftment success (100%) and sustained clinical improvements.

The primary efficacy endpoints demonstrate profound and durable therapeutic benefit. Overall survival of 96% (95% CI: 82-99) compares favorably to published HSCT outcomes (83.3% in literature reviews), with the single death being unrelated to the GT product. Severe infections decreased from 2.00 events per person-year pre-treatment to 0.16 events per person-year in the 6 to 18-month period and 0.09 events per person-year in the >6 month follow-up period, representing a 95% reduction. Similarly, moderate and severe bleeding events decreased from 2.00 events per person-year pre-treatment to 0.80 events per person-year in the first 12 months and 0.03 events per person-year in the >4-year period.

The mechanism underlying these clinical improvements is the restoration of WASP expression across all hematopoietic cell lineages. Wiskott-Aldrich syndrome protein expression increased in platelets (14.3% to 77.2% by Day 180) and progressively in lymphocytes (3.9% to 72.4% by Year 2), reaching sustained levels of 60% to 80%. This biological restoration translated into normalized T-cell function, with proliferative responses increasing from severely impaired baseline levels (median stimulation index 30.2) to normal ranges (>150) by Year 2 and continuing to improve through Year 8 (210.7). The functional improvements enabled successful discontinuation of supportive therapies in the vast majority of patients: 92% achieved cessation of IgRT, 85% discontinued sustained antimicrobial treatment, and 100% achieved platelet transfusion independence.

Subpopulation analyses reveal that WASKYRA's efficacy is consistent across diverse patient populations and manufacturing parameters.

The sustained improvements enabled quality of life enhancements: patients transitioned from protective isolation to normal social activities, with 100% attending school by later timepoints and the majority participating in sports. The resolution of eczema in all patients by Year 6, normalization of social life, and elimination of the need for chronic medical interventions represent improvement in quality of life for patients and families previously facing a life-threatening progressive disease.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

An assessment of safety was conducted by analyzing all patients treated in the WASKYRA clinical development program.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database includes 27 patients with WAS treated with WASKYRA in Studies TIGET-WAS and OTL-103-4, as well as two expanded access studies. All 27 patients were exposed to a one-time intravenous infusion of WASKYRA. The median age at treatment was 2.56 years (range: 0.98-35.1 years). The median dose was 16.9×10^6 cells/kg (range: 7.0-30.9 cells/kg). The median duration of follow up in the pooled analyses was 5.67 years (range: 0.37-13.26 years). Two patients in the EAP, (b) (6) and (b) (6), had undergone splenectomy prior to GT.

One patient did not receive the WASKYRA infusion and was withdrawn because the target dose of CD34+ cells was not reached after leukapheresis. This patient was excluded from Safety population.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The Safety population consists of 27 patients who were exposed to a one-time intravenous infusion of WASKYRA. All patients were males diagnosed with WAS. The median age at treatment was 2.56 years (range, 0.98-35.1 years). Only two patients treated in the EAP were adults at the time of treatment, 28 and 35 years old. All pediatric patients treated in WASKYRA

clinical development program were younger than 16 years old at treatment. The median duration of follow up in the pooled analyses was 5.67 years (range, 0.37-13.26 years).

Table 10 provides demographics and baseline disease characteristics for all patients in the Safety population.

Table 10: Study Population Data, Safety Population

Demographic and Baseline Characteristics		(N=27)
Age at Gene Therapy		-
Mean (SD)		6.3 (8.3)
Median		2.6
(Min, max)		(0.98, 35.1)
Race, n (%)		-
American Indian or Alaska Native		1 (3.7)
Asian		4 (14.8)
Black or African American		2 (7.4)
White		20 (74.1)
Ethnicity, n (%)		-
Hispanic or Latino		3 (11.1)
Not Hispanic or Latino		24 (88.9)
Zhu score at baseline, n (%) ^a		-
2.0		1 (3.7)
3.0		13 (48.1)
4.0		4 (14.8)
5.0A		8 (29.6)
WAS gene mutation, n (%)		-
Class I		5 (18.5)
Class II		22 (81.5)
WASP expression at baseline, n (%)		-
Missing ^b		1 (3.7)
Absent		15 (55.6)
Presence of revertant (>5%) ^c		1 (3.7)
Present		7 (25.9)
Reduced		3 (11.1)

Source FDA statistical reviewer

^a A baseline Zhu score of 5.0A in one patient was windowed to the treatment visit because it was assessed after the start of mobilization for peripheral blood stem cell collection

^b "WASP expression in total lymphocytes at baseline" category was missing for one patient in Study OTL- 103-4.

^c The presence of a cell population expressing normal levels of WASP and representing >5% of lymphocytes was classified as revertant.

Abbreviations: max, maximum; min, minimum; n (%), number of patients with the specified characteristic; N, number of patients in the specified group, or the total sample; WAS, Wiskott-Aldrich syndrome; WASP, Wiskott-Aldrich syndrome protein

8.2.2.1 Exposure to Rituximab and Reduced Intensity Conditioning Regimen

All 27 patients received rituximab and RIC regimen. The median rituximab dose was 200 mg. The median total dose of fludarabine was 60 mg/m², and the median total dose of busulfan was 9.338 mg/kg. The median cumulative AUC of busulfan was 49,856 ng·h/mL (Table 11).

Exposure to busulfan was higher than the target range of cumulative AUC of 48,000 ng·h/mL(±10%) in 7 of the 10 patients in Study OTL-103-4. In particular, the respective estimated cumulative AUCs of busulfan were 54,108 ng·h/mL for Patient (b) (6), 55,524.00 ng·h/mL for Patient (b) (6), 81,012ng·h/mL for Patient (b) (6), 62,704 ng·h/mL for Patient (b) (6), 49,856.00 ng·h/mL for Patient (b) (6), and 52,774.83 ng·h/mL for Patient (b) (6).

Table 11: Exposure to Rituximab and Conditioning Regimen

Characteristic	Rituximab (mg) (N=27)	Busulfan (Total Dose mg/kg) (N=27)	Fludarabine (Total Dose mg/m ²) (N=27)
Number (%) of patients who received treatment	27(100)	27(100)	27(100)
Total dose administered	-	-	-
Median	200.00	9.338	60.000
Min-max	4.3–700.0	5.87–14.74	55.56–61.54
Cumulative AUC (ng·h/mL)	-	-	-
Median	NA	49,856.00	NA
Min-max	NA	33,313.60–81,012.00	NA

Source: Adapted from BLA submission Summary of Clinical Efficacy

Abbreviations: AUC, area under the curve; max, maximum; min, minimum; N, number of patients in the specified group, or the total sample; NA, not applicable

8.2.2.2 Exposure to WASKYRA

For the 27 patients that received WASKYRA infusion, the median total volume of WASKYRA infused was 30.50 mL. All patients received an adequate drug product dose (Table 12). The median dose of CD34+ cells infused was 16.90×10⁶/kg. Transduction efficiency was >80% in 21 of 27 (77.8%) patients, and the median VCN per cell in the drug product was 2.30 VCN/cell. One patient received a dose of CD34+ cells of 30.9×10⁶/kg, slightly outside the recommended range of 3 to 30×10⁶/kg CD34+ cells, in the OTL-103-4 clinical study.

Table 12: Exposure to WASKYRA

Characteristic	WASKYRA (N=27) Median (Min-Max)
Total volume infused (mL)	30.50 (19.6–120.0)
Total nucleated cells (10 ⁶)	277.5 (92–1188)
Number of nucleated cells (10 ⁶ /kg)	17.10 (7.1–31.6)
Number of CD34+ cells (10 ⁶ /kg)	16.90 (7.0–30.9)
Percentage of CD34+ cells ^a	96.62 (71.6–99.2)
Number of CFU-GM (10 ⁶ cells)	46,000.0 (0–144,000)
Transduction efficiency (%)	-
≤80, n (%)	6 (22.2)
>80, n (%)	21 (77.8)
VCN/cell	2.30 (0.9–4.3)

Source: Adapted from BLA submission Summary of Clinical Efficacy

^a Percentage of CD34+ cells was calculated as (number of infused CD34+/kg)/number of nucleated cells/kg×100.

Abbreviations: CD, cluster of differentiation; CFU-GM, colony forming units-granulocyte/macrophage; max, maximum; min, minimum; mPB, mobilized peripheral blood; N, number of patients in the specified group, or the total sample; VCN, vector copy number

8.2.3 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Mobilized PB was the CD34+ cell harvest source of WASKYRA for most patients (21 [77.8%]); the cell harvest source was BM for 5 (18.5%) patients, and was a combination of BM and mPB for 1 (3.7%) patient. Ten patients received the cryopreserved formulation of WASKYRA sourced from mPB, and 17 patients received the fresh formulation of WASKYRA (sourced from BM and/or mPB).

Reviewer Comment: *The cryopreserved formulation contains DMSO ,which could cause hypersensitivity reaction. No hypersensitivity reaction related to WASKYRA was observed in patients treated with either formulation. No AEs were considered related to WASKYRA. It is considered appropriate to pool safety data from different cell harvest sources and both formulations.*

8.4 Safety Results

8.4.1 Deaths

Patient (b) (6) is a 35-year-old White male who had been diagnosed with WAS at the age of 2 years, died approximately 4.5 months after receiving WASKYRA infusion in EAP due to a deterioration of a preexisting neurological condition (SAE preferred term: neurological decompensation; verbatim term: neurological deterioration). The patient had a medical history of spastic gait that was ongoing at screening, and a Grade 3 AE of neurodegenerative disorder (verbatim term: neurodegeneration with brain iron accumulation) with onset on Day -185. This patient's death was not considered to be related to WASKYRA by the treating physician or the Applicant; however, relatedness to the conditioning regimen could not be excluded.

8.4.2 Nonfatal Serious Adverse Events

Sixty-seven SAEs were reported in 22 (81.5%) patients from RIC to the last follow up visit. Serious adverse events affecting at least two patients are shown in Table 13. None of the SAEs were considered related to WASKYRA. One SAE of papillary thyroid cancer was resolved with sequelae. One SAE of congenital coronary artery malformation was considered not recovered/resolved. One SAE of neurological decompensation was fatal. All other SAEs were recovered/resolved. The majority of SAEs occurred in the first 6 months after WASKYRA infusion (35 events in 18 [66.7%] patients).

Reviewer Comment: *The narrative summaries of all SAEs were reviewed. The reviewers agree with the Applicant's and investigators' assessments.*

Table 13: Nonfatal Serious Adverse Events Affecting ≥Two Patients

SAE	n (%) (N=27)
Device related infection ^a	11 (40.7)
Pyrexia	5 (18.5)
Gastroenteritis ^b	3 (11.1)
Sepsis ^c	2 (7.4)
Cellulitis	2 (7.4)
Neutropenia ^d	2 (7.4)
Pneumonia ^e	2 (7.4)
Vomiting	2 (7.4)

Source: FDA

^a Device related infections include catheter site abscess, catheter site infection, device related infection and device related sepsis.

^b Gastroenteritis includes gastroenteritis, gastroenteritis *Escherichia coli*, gastroenteritis rotavirus, gastroenteritis salmonella, gastroenteritis viral, gastrointestinal bacterial infection, gastrointestinal infection, and hemorrhagic gastroenteritis.

^c Sepsis includes bacterial sepsis and pseudomonal sepsis.

^d Neutropenia includes autoimmune neutropenia, febrile neutropenia, neutropenia, neutrophil count decreased.

^e Pneumonia includes pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal and pneumonia staphylococcal.

Abbreviations: n (%), number of patients with the specified characteristic; N, number of patients in the specified group, or the total sample; SAE, serious adverse event

8.4.3 Study Dropouts/Discontinuations

There were no AEs leading to study discontinuation. Discontinuation of investigational medicinal product was not applicable, as WASKYRA was administered as a single infusion; therefore, it could not be discontinued.

8.4.4 Common Adverse Events

A total of 1,993 AEs were reported between pre-conditioning (Day -22), RIC and the last study follow up visit. All patients experienced at least one AE during this period. The most common AEs were upper respiratory tract infection (23 [85.2%]), anti-platelet antibody positive (20 [74.1%]), pyrexia (20 [74.1%]), anemia (19, [70.4%]), diarrhea (18 [66.7%]), eczema (18 [66.7%]), livery injury (18 [66.7%]), and petechiae (18 [66.7%]). None of the AEs were considered related to WASKYRA. Adverse events affecting at least 30% of patients are listed in Table 14.

Table 14: Adverse Events Affecting ≥30% of Patients

Adverse Event	n (%) (N=27)
Upper respiratory tract infection ^a	23 (85.2)
Anti-platelet antibody positive ^b	20 (74.1)
Pyrexia	20 (74.1)
Anemia ^c	19 (70.4)
Diarrhea ^d	18 (66.7)
Eczema ^e	18 (66.7)
Liver injury ^f	18 (66.7)
Petechiae	18 (66.7)
Coronavirus infection ^g	17 (63.0)
Rash ^h	17 (63.0)
Device related infection ⁱ	16 (59.3)
Rhinitis	16 (59.3)
Cough ^j	14 (51.9)
Conjunctivitis ^k	13 (48.1)
Vomiting	13 (48.1)
Ear infection ^l	12 (44.4)
Epistaxis	12 (44.4)
Gastroenteritis ^m	12 (44.4)
Head injury	11 (40.7)

Adverse Event	n (%) (N=27)
Neutropenia ⁿ	11 (40.7)
Blood immunoglobulin E increased	9 (33.3)
Vitamin D decreased	9 (33.3)

Source: FDA

^a Upper respiratory tract infection includes pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, upper respiratory tract infection, viral upper respiratory tract infection, nasal vestibulitis, nasopharyngitis, laryngitis, laryngitis viral, laryngopharyngitis.

^b Anti-platelet antibody positive includes anti-platelet antibody positive and anti-platelet antibody.

^c Anemia includes Anemia, autoimmune hemolytic anemia, hemolytic anemia, coombs direct test positive, coombs indirect test positive, iron deficiency anemia.

^d Diarrhea includes diarrhea, diarrhea hemorrhagic, diarrhea infectious.

^e Eczema includes dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, catheter site eczema, dyshidrotic eczema, eczema, eczema eyelids, eczema herpeticum.

^f Liver injury includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hypertransaminasemia, transaminases increased, drug-induced liver injury.

^g Coronavirus infection includes coronavirus infection and COVID-19.

^h Rash includes rash, rash erythematous, rash maculo-papular, rash popular, rash pruritic, rash pustular, rash vesicular, genital rash, urticaria, administration site urticaria, catheter site pruritus, pruritus.

ⁱ Device related infections include catheter site abscess, catheter site infection, device related infection and device related sepsis.

^j Cough includes cough and productive cough.

^k Conjunctivitis includes conjunctival hemorrhage, conjunctival hyperemia, conjunctivitis, conjunctivitis allergic and conjunctivitis bacterial.

^l Ear infection includes ear infection, ear infection fungal, ear pain, otitis externa, otitis media and otitis media acute.

^m Gastroenteritis includes gastroenteritis, gastroenteritis *Escherichia coli*, gastroenteritis rotavirus, gastroenteritis salmonella, gastroenteritis viral, gastrointestinal bacterial infection, gastrointestinal infection, and hemorrhagic gastroenteritis.

ⁿ Neutropenia includes autoimmune neutropenia, febrile neutropenia, neutropenia, neutrophil count decreased.

Abbreviations: n (%), number of patients with the specified characteristic; N, number of patients in the specified group, or the total sample

A total of 210 High Grade AEs (\geq Grade 3) were reported in 25 (92.6%) patients between RIC and the last study follow up visit. The most common severe AEs affecting at least 20% of patients were device-related infection (14 [51.9%]), neutropenia (9 [33.3%]), pyrexia (8 [29.6%]), and rash (6 [22.2%]).

8.4.5 Clinical Test Results

8.4.5.1 Vital Signs

There were no notable observations in systolic or diastolic blood pressure, pulse rate, or body temperature over time.

Temperature

Adverse events of pyrexia are shown in the tables of [Section 8.4.4](#). No instances of low temperature $<35^{\circ}\text{C}$ were reported.

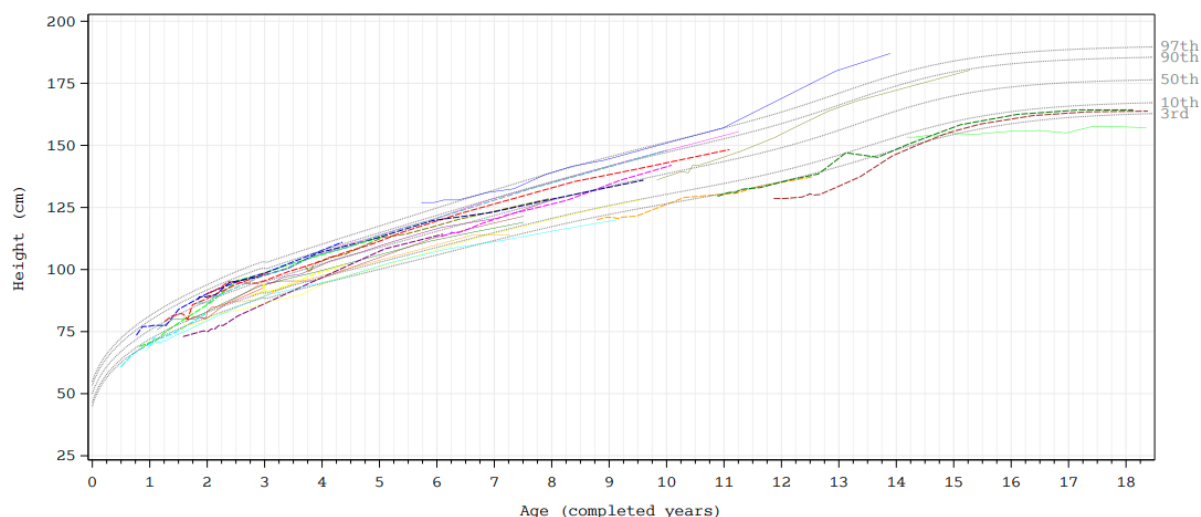
Blood Pressure

Out-of-range blood pressure values were reported as mild to moderate AEs of hypertension in one patient (3.7%) in the pre-treatment phase, two patients (7.4%) during conditioning, and one patient (3.7%) in the post-treatment phase. In addition, a moderate AE of pulmonary hypertension was reported in one (3.7%) patient in the 0 to 6-month post-treatment phase, as a complication following acute respiratory distress syndrome. All of the AEs resolved.

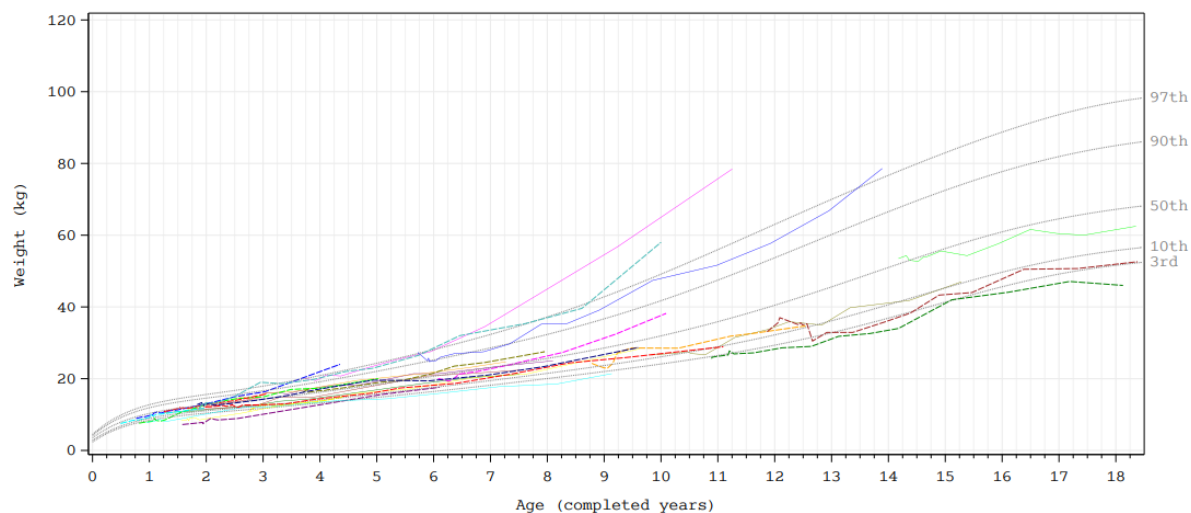
Height and Weight

Patients generally continued to track along their original percentiles for height and weight ([Figure 10](#)).

Figure 10: Individual Profiles of Physical Growth (Height and Weight) Over Time



(b) (6)



(b) (6)

Source: BLA 125846 Summary of Clinical Safety

Note: Abbreviated patient identifiers were used to label data points. 'TWXX'=Study TIGET-WAS patient, 'HEXX'=HE patient, 'CUPXX'=CUP patient, 'OTLXX'=OTL-103-4 patient, (b) (6)=Study OTL-103-4 Children's Healthcare of Atlanta (CHOA)/Emory University School of Medicine site patient (b) (6).

Patient data only included up to the age of 19 years. Adult patients in EAP were not included in the plot.

Percentiles were based on World Health Organization (WHO) height and weight growth charts (WHO, 2006).

Abbreviations: CUP, Compassionate Use Program; HE, Hospital Exemption

Weight at baseline ranged from 7.59 kg to 70 kg with a median of 13.46 kg. Weight gain was slow in patient (b) (6) from approximately 3.5 years after WASKYRA infusion, and this was reported as a Grade 1 AE of poor weight gain in the 3 to 8-year period (the event resolved after duration of 5 years). Patient (b) (6) rose rapidly between 6 months and 1 year after WASKYRA infusion, and this was reported as an AE of obesity in the 1 to 2-year period (Grade 3 reducing to a Grade 2 event, which then resolved). Patient (b) (6) had a further AE of obesity in the >8 years period, which was ongoing at the time of reporting (initially Grade 2, increasing to Grade 3, and then decreasing to Grade 1).

8.4.5.2 Complete Blood Count

Values for hematocrit, hemoglobin, and leukocytes decreased after the start of treatment, as expected due to conditioning. Hematocrit and hemoglobin subsequently returned to baseline levels by around Day 180 (6 months post-treatment), and leukocyte count returned to baseline levels by Day 90 (3 months post-treatment). Values for other hematology parameters such as erythrocytes, lymphocytes, and neutrophils also decreased after the start of treatment, and median values generally returned to baseline levels by around Year 1, with mean neutrophil count markedly increased (compared with the values recorded during the earlier post-treatment visits) by Day 90 and close to baseline by Year 2.5.

Platelet counts are assessed as part of the efficacy analyses and discussed in [Section 7.1.5](#). Delayed neutrophil is considered an AE of special interest and is reviewed in [Section 8.4.8](#).

8.4.5.3 Clinical Chemistries

Liver function test values such as ALT and AST tended to increase transiently over a period of 3 to 6 months following conditioning and WASKYRA infusion, but generally remained below 2×upper limit of normal (ULN), with two patients with ALT values >2×ULN and <5×ULN; and six patients with AST values >2×ULN and <5×ULN. Liver function test values subsequently returned to baseline levels by around Day 180. Abnormal liver function test values reported as AEs are discussed in [Section 8.4.4](#).

Transient shifts from normal at baseline to high post-treatment were observed in ≥50% of patients for D-dimer, ALT, AST, gamma-glutamyl transferase, C-reactive protein, lactate dehydrogenase, and glucose.

Frequently reported AEs ≥30% patients related to clinical chemistry findings are discussed in [Section 8.4.4](#). Hypokalemia was reported in eight (29.6%) patients during conditioning and post-treatment period.

8.4.6 Systemic Adverse Events

Refer to the discussion of AEs in [Section 8.4.4](#).

8.4.7 Local Reactogenicity

There was no evidence of local reactogenicity in this submission.

8.4.8 Adverse Events of Special Interest

8.4.8.1 Prolonged Neutropenia

Two patients experienced prolonged neutropenia SAEs following WASKYRA treatment.

Patient (b) (6) presented with severe neutropenia ($<500/\mu\text{L}$) 10 days after GT, which was expected after conditioning. The patient's neutrophil count remained less than $200/\mu\text{L}$ from Day 11, dropped to 0 from Day 18 to Day 22, rose to $100/\mu\text{L}$ on Day 23, then dropped to 0 on Day 25. On Day 46, the patient was diagnosed with prolonged neutropenia (Grade 4), owing the persistent low levels of neutrophils and no response to filgrastim (G-CSF). An unscheduled BM aspirate was performed, which revealed a slowing maturation of the myeloid compartment and eosinophilia; however, there were good levels of transduction in most BM lineages (including myeloid). All virological tests were negative. Anti-neutrophil antibodies were positive on Day 52. The patient subsequently received methylprednisolone, antibiotic prophylaxis, rituximab, and off-label eltrombopag (with informed consent). The patient was discharged in good clinical condition on Day 85. Laboratory tests at discharge revealed: white blood cell count $8,400/\mu\text{L}$, neutrophil count $6.2 \times 10^9/\text{L}$ (ref: 1.5-8.0), lymphocyte count $900/\mu\text{L}$, monocyte count $900/\mu\text{L}$, eosinophil count $500/\mu\text{L}$, Hb 9.0 g/dL, and platelet count $52,000/\mu\text{L}$. On June 24, 2020, the outcome of the event of autoimmune neutropenia was considered recovered/resolved.

Patient (b) (6) started to experience severe neutropenia (neutrophil count less than $500/\mu\text{L}$) 8 days after WASKYRA treatment. The patient experienced 26 days with neutrophil counts less than $200/\mu\text{L}$ (the exact neutrophil count and dates were not provided). The patient's neutrophil count was $380/\mu\text{L}$ on Day 47, and GT hospitalization was therefore prolonged. Granulocyte-colony stimulating factor was not administered because the patient was in good clinical condition, especially as the normal differentiation of the different hematopoietic lineages in the BM (as observed at aspiration performed at Day 30 post-treatment from the GT), the good engraftment level of transduced cells, and the improving trend of neutrophils that oscillated around the value of $500/\mu\text{L}$. On Day 63, the patient was discharged in good clinical condition, and the outcome of the event of prolonged neutropenia was considered resolved/recovered.

Reviewer Comment: *The prolonged neutropenia was considered not related to WASKYRA, but relatedness to RIC cannot be ruled out. Risk of prolonged neutropenia is described in warnings and precautions section in the product label.*

8.4.8.2 Immune-Mediated Adverse Events

Forty immune-mediated AEs were reported in 9 (33.3%) patients in the post-treatment phase, and 2 events in 2 (7.4%) patients during conditioning ([Table 15](#)).

Table 15: Patients with Immune-Mediated Adverse Events by System Organ Class, Preferred Term, and Treatment Phase, Safety Population

System Organ Class Dictionary-Derived Term	1: Pre- Treatment (N=27)	2: On- Treatment (N=27)	3: 0-6 Months (N=26)	4: 6-12 Months (N=26)	5: 1-2 Years (N=26)	6: 2-3 Years (N=22)	7: 3-8 Years (N=21)	8: >8 years (N=8)	Post- Treatment (N=27)
Patients with AE	5 (18.5) 7	2 (7.4) 2	6 (23.1) 6	1 (3.8) 1	0	0	5 (23.8) 17	1 (12.5) 16	9 (33.3) 40
Blood and lymphatic system disorders	1 (3.7) 1	0	5 (19.2) 5	0	0	0	1 (4.8) 1	0	5 (18.5) 6
Immune thrombocytopenia	1 (3.7) 1	0	4 (66.7) 4	0	0	0	0	0	4 (14.8) 4
Autoimmune neutropenia	0	0	1 (3.8) 1	0	0	0	0	0	1 (3.7) 1
Thrombosis with thrombocytopenia syndrome	0	0	0	0	0	0	1 (4.8) 1	0	1 (3.7) 1
Endocrine disorders	0	0	0	0	0	0	1 (4.8) 1	0	1 (3.7) 1
Graves' disease	0	0	0	0	0	0	1 (4.8) 1	0	1 (3.7) 1
Gastrointestinal disorders	0	0	0	1 (3.8) 1	0	0	1 (4.8) 2	0	2 (7.4) 3
Colitis ulcerative	0	0	0	0	0	0	1 (4.8) 2	0	1 (3.7) 1
Crohn's disease	0	0	0	1 (3.8) 1	0	0	0	0	1 (3.7) 1
Immune system disorders	0	1 (3.7) 1	0	0	0	0	1 (4.8) 1	0	1 (3.7) 1
Autoinflammatory disease	0	1 (3.7) 1	0	0	0	0	0	0	0
Hypogammaglobulinaemia	0	0	0	0	0	0	1 (4.8) 1	0	1 (3.7) 1
Musculoskeletal and connective tissue disorders	1 (3.7) 1	0	0	0	0	0	0	0	0
Sjogren's syndrome	1 (3.7) 1	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	2 (7.4) 2	0	0	0	0	0	0	1 (12.5) 1	1 (3.7) 1
Cutaneous vasculitis	1 (3.7) 1	0	0	0	0	0	0	0	0
Henoch-Schonlein purpura	0	0	0	0	0	0	0	1 (12.5) 1	1 (3.7) 1
Psoriasis	1 (3.7) 1	0	0	0	0	0	0	0	0
Vascular disorders	2 (7.4) 3	1 (3.7) 1	1 (3.8) 1	0	0	0	1 (4.8) 12	1 (12.5) 15	2 (7.4) 28
Vasculitis	2 (7.4) 3	1 (3.7) 1	1 (3.8) 1	0	0	0	1 (4.8) 12	1 (12.5) 15	2 (7.4) 28

Source: FDA

Abbreviations: AE, adverse event; n (%), number of patients with the specified characteristic; N, number of patients in the specified group, or the total sample

Within 6 months of WASKYRA infusion, one patient experienced autoimmune neutropenia (discussed in [Section 8.4.8.1](#)). Four patients experienced immune thrombocytopenia, as described below.

Patient (b) (6) had a Grade 3 AE of immune thrombocytopenia in the first 6 months after WASKYRA infusion, which resolved after 29 days following treatment with high-dose intravenous immunoglobulins.

Patient (b) (6) had a Grade 4 clinical manifestation of immune thrombocytopenia from over 2 years before GT (recorded in medical history), which resolved within the first 6 months following WASKYRA infusion.

Patient (b) (6) had a Grade 3 (nonserious) AE of immune thrombocytopenia (verbatim term: autoimmune thrombocytopenia) during the first 6 months after WASKYRA infusion. This event was reported on Day 84, was treated with high-dose intravenous Ig and intravenous rituximab, and resolved with sequelae after 176 days (on Day 259).

Patient (b) (6) had reported hemolytic anemia and immune thrombocytopenia 7 to 8 years before WASKYRA treatment. In the first 6 months after WASKYRA infusion, Patient (b) (6) had a severe event of autoimmune thrombocytopenia, which resolved within the first year post-treatment.

One event of thrombosis with thrombocytopenia syndrome (verbatim term: post-vaccination thrombocytopenia) occurred in Patient (b) (6) that was reported in the 3 to 5-year period after WASKYRA infusion and was not classed as an SAE.

Reviewer Comment: *Overall, the immune-mediated events reported were expected considering the background disease of patients (especially for Patient (b) (6) who had a comorbidity of inherited familial Mediterranean fever) and the effects of conditioning, and generally resolved within the post-treatment phase.*

8.4.8.3 Veno-Occlusive Liver Disease

Veno-occlusive liver disease is recognized as a known complication of busulfan conditioning. Veno-occlusive liver disease occurred in one patient. Patient (b) (6) experienced a SAE of VOD that occurred on Day 9 and resolved on Day 42. Both the AE of hepatic enzyme increased and the SAE of VOD were considered by the investigator to be related to the conditioning regimen and did not meet Hy's law criteria.

8.4.8.4 Risk of Insertional Oncogenesis

Given that lentiviral GT products integrate into the genome of the patients, insertional oncogenesis is a potential risk of WASKYRA. Additionally, events of insertional oncogenesis have been seen in use of other lentiviral GT products. There were no reported events of abnormal clonal proliferation, leukemia, or lymphoproliferation following WASKYRA infusion.

8.4.8.5 Replication-Competent Lentivirus

Results of RCL testing were negative in all patients.

An HIV-1 viral load (RNA) test was performed in error at Year 1 post-WASKYRA infusion in Patient (b) (6). This test result was positive as expected, while this patient was negative for RCL testing through determination of HIV-1 p24 antigen or HIV-1 p24 binding antibody. This test should not have been performed after GT, as the commercially available tests to detect HIV-1-polymerase RNA are unable to differentiate between the DNA of genetically corrected cells and HIV-1 infection, leading to increased risk of false positive results.

8.4.8.6 Hypersensitivity

Given the presence of DMSO in the drug product suspension, there is a risk of allergic reactions, including anaphylaxis. There were no reported events of serious hypersensitivity reactions that occurred during WASKYRA infusion.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Determination of dose dependency for AEs is challenging in this small Safety population. The dose administered to each individual patient was based on the number of cells harvested during apheresis. There are two ways to consider dose: the first is in the number of CD34+ cells administered per kilogram of body weight, while the second is the total number of CD34+ cells administered. No trends in dose and AEs (incidence or severity) were observed.

8.5.2 Time Dependency for Adverse Events

Given administration of the myeloablative conditioning regimen, serious infections may occur prior to immune reconstitution is achieved. Of the 27 WASKYRA-treated patients, 18 (66.7%) experienced 35 serious infections in the 6 months following WASKYRA infusion.

Most thrombocytopenia and prolonged neutropenia occurred within the first 3 months following WASKYRA infusion.

Table 16: Number of Patients with Adverse Events by Treatment Phase, Safety Population

Adverse Event	0-6 Months (N=27)	6-12 Months (N=26)	1-2 Years (N=26)	2-3 Years (N=22)	3-8 Years (N=21)	>8 Years (N=8)	Post-Treatment (N=27)
Any AE	27 (100) 571	25 (96.2) 150	26 (100) 260	22 (100) 189	21 (100) 562	8 (100) 122	27 (100) 1854
Any AE Grade ≥3	22 (81.5) 125	5 (19.2) 7	6 (23.1) 11	7 (31.8) 10	7 (33.3) 13	2 (25.0) 3	22 (81.5) 169
SAE	18 (66.7) 35	4 (15.4) 4	4 (15.4) 5	5 (22.7) 6	6 (28.6) 8	2 (25.0) 2	18 (66.7) 60

Source: FDA

Abbreviations: AE, adverse event; N, number of patients in the specified group, or the total sample; SAE, serious adverse event

8.5.3 Product-Demographic Interactions

The ability of the data to determine product-demographic interactions is challenging due to the small size of the study population. No notable differences in safety profiles were observed in the sub-analyses of data based on age in pediatric patients treated with WASKYRA. One of the two adult patients who were treated in the EAP died (see [Section 8.4.1](#)).

8.5.4 Product-Product Interactions

No drug interaction studies were conducted.

8.5.5 Human Carcinogenicity

Given that WASKYRA uses an LVV, insertional oncogenesis is a potential risk of treatment. However, no cases of insertional oncogenesis or clonal expansion were observed in the study population.

A patient with a family history of nonmalignant thyroid disease (Patient (b) (6)) experienced high levels of thyroid-stimulating hormone receptor antibodies, referred to as Graves' disease (verbatim term: autoimmune hyperthyroidism) at 5 years post-GT and was subsequently diagnosed with an SAE of papillary thyroid cancer. The DNA extracted from tumor cells did not contain viral vector gene sequences, with the exception of a minor contaminant that was found at a comparable level also in normal thyroid tissue tested in parallel. The investigator therefore did not consider this neoplasia involving cells of not hematopoietic origin as related to WASKYRA, but as possibly related to conditioning and the long history of previous immune suppression in this patient. Thyroid papillary carcinoma is a known secondary tumor that can occur after HSCT, likely favored by conditioning regimen and possibly immune suppression. The event resolved with sequelae (i.e., iatrogenic hypothyroidism following total thyroidectomy).

8.5.7 Immunogenicity (Safety)

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

8.5.8 Person-to-Person Transmission, Shedding

Person-to-person transmission and viral shedding do not appear to be risks with WASKYRA.

8.5.9 One-Hundred Twenty-Day Safety Update

The updated Integrated Summary of Safety only contains new AEs from the ongoing OTL-103-4 study. The Applicant stated that for Study WAS-TIGET and HE/CUP, the clinical database was closed, and the respective study/program completed; hence no further information is updated for these programs in version 2.0 of Integrated Summary of Safety.

Patient Disposition

- No new patients were enrolled.
- All 26 (increased from 24) surviving patients now have completed, at minimum, 2 years of follow-up after WASKYRA infusion. Twenty-four patients completed the Year 3 visit (increased from 22).

Adverse Events

Sixty-three new AEs were reported in the safety update. Newly reported AEs were mainly in the system organ class of infections/infestations (30 new AEs) and Investigations (9 new AEs). The majority of new reported AEs were of mild (n=25) or moderate (n=37) severity. No new SAEs were reported. No new cases of malignancy were reported. No new immune-mediated AEs were reported.

Reviewer Comment: *It appears that there is no change in the overall safety profile with the 120-day safety update. The updated dataset was not included in this review.*

New Patients Treated in EAP

It was noted in the Applicant's response to a clinical information request regarding the 120-day safety update that between December 2023 and May 2025, a total of 6 patients with WAS had been treated with WASKYRA in the context of an early access program according to Italian 648/1996 law. The median age of patients at treatment was 2.3 years (range: 1.0-5.4) and median follow up as of June 16, 2025, is 0.8 years (range: 0.1-1.5). Four SAEs of catheter infections (n=2), catheter site bleeding, and hyperleukocytosis were reported in three of the six patients. Three of the SAEs—catheter infection, catheter site bleeding and hyperleukocytosis—occurred before infusion of WASKYRA. All four SAEs were considered not related to WASKYRA and resolved.

8.6 Safety Conclusions

The most common adverse reactions reported in the WASKYRA clinical development program included eczema (17 [63.0%]), device-related infection (16 [59.3%]), liver injury (16 [59.3%]), petechiae (16 [59.3%]), rash (16 [59.3%]), and upper respiratory tract infection (14 [51.9%]). These adverse reactions are not unexpected, as they are either part of the disease, known toxicity, or high-risk events associated with myeloablative regimen.

The death of an adult patient due to neurological decompensation was unexpected. The death was considered unrelated to WASKYRA but relatedness to conditioning regimen cannot be ruled out. Of note, only two adult patients were treated in the WASKYRA clinical development program. Safety of WASKYRA treatment including the required conditioning regimen in adult patients with WAS were limited and not interpretable.

The SAE of papillary thyroid cancer was unexpected and not related the WASKYRA. No AE of insertional mutagenesis was reported.

Serious adverse events of prolonged neutropenia occurred in two patients within the first 30 days following WASKYRA treatment and were not unexpected. The SAE of VOD was also not unexpected, as it is a known toxicity of busulfan conditioning. All three SAEs resolved. Monitoring of such events during conditioning and within the first month following WASKYRA infusion is advised.

Results of RCL testing were negative in all patients. One patient tested positive for HIV by reverse-transcription polymerase chain reaction, while this patient was negative for RCL testing through determination of HIV-1 p24 antigen or HIV-1 p24 binding antibody. Human immunodeficiency virus testing by reverse-transcription polymerase chain reaction after WASKYRA treatment is not recommended, as the test may not be able to differentiate between the DNA of genetically corrected cells and HIV-1 infection, leading to increased risk of false positive results.

Immune related AEs, including immune thrombocytopenia and autoimmune neutropenia, are expected, as patients with WAS have high risks to develop autoimmunity.

Overall, WASKYRA demonstrates an acceptable safety profile.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

WAS is an X-linked recessive disorder that primarily affects males. No females, including pregnant and breastfeeding females, received WASKYRA.

9.1.2 Use During Lactation

WAS is an X-linked recessive disorder that primarily affects males. No females, including pregnant and breastfeeding females, received WASKYRA.

9.1.3 Pediatric Use and PREA Considerations

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

9.1.4 Immunocompromised Patients

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

9.1.5 Geriatric Use

The safety and efficacy of WASKYRA in geriatric patients with WAS have not been studied.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

None.

10. CONCLUSIONS

In summary, the clinical review team concludes that there is substantial evidence of a favorable benefit-risk for use of WASKYRA for the treatment of patients 6 months and older with WAS who have a mutation in the WAS gene and for whom hematopoietic stem cell transplantation (HSCT) is appropriate and no suitable HLA-matched related stem cell donor is available.

WASKYRA demonstrated substantial clinical benefits across 27 patients with severe WAS, achieving an OS rate of 96% with median follow-up of 5.67 years extending up to 13.26 years. The treatment provided a clinically meaningful reductions in the hallmark manifestations of WAS, with severe infections rate reducing from 2.00 events per person-year pre-treatment to 0.16 events per person-year in the 6 to 18-month period post-treatment, sustained at 0.09 events per person-year long-term. Similarly, moderate and severe bleeding events decreased from 2.00 events per person-year pre-treatment to 0.80 events in the first 12 months, and further to 0.03 events per person-year after 4 years. Platelet recovery was achieved, with median counts increasing from $18.00 \times 10^9/L$ at baseline to $59.00 \times 10^9/L$ at Year 1, enabling

complete independence from platelet transfusions. The treatment restored immune system function, normalized T-cell responses, enabled successful vaccination including live-attenuated vaccines, and allowed cessation of IgRT and antimicrobial prophylaxis.

The quality-of-life improvements included patients achieving independence from continuous supportive treatments and experiencing reduced hospitalizations from 2.85 to 0.17 events per person-year. Patients were able to normalize social activities including school attendance and sports participation, with no patients requiring protected environments beyond Year 3.

Several SAEs were attributed to conditioning, including neutropenia, VOD, and suspected thrombotic microangiopathy, particularly in patients with unexpectedly high busulfan exposure. One fatal case occurred due to deterioration of a preexisting neurological condition, with a possible but uncertain relationship to conditioning. Patients experienced increased vulnerability to infections during the first 6 months post-treatment due to immune system reconstitution, requiring careful monitoring and supportive care during this period.

Long-term safety monitoring identified one case of papillary thyroid cancer occurring 5 years post-treatment, which was considered possibly related to conditioning and prior immunosuppression rather than WASKYRA itself. No AEs were directly attributed to WASKYRA, with no detection of RCL, no evidence of insertional mutagenesis, and no immunogenicity against WASP observed over up to 13.26 years of follow-up.

While treatment-related procedures carry manageable risks typical of stem cell transplantation, these are substantially outweighed by the benefits of disease correction and the prevention of life-threatening complications. The benefit-risk profile of WASKYRA is favorable for patients with severe WAS who lack suitable HLA-matched related donors.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk benefit considerations are shown below in [Table 17](#).

Table 17: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • WAS is a rare, X-linked primary immune deficiency and platelet disorder characterized by microthrombocytopenia, eczema, recurrent infections, and increased susceptibility to autoimmunity and lymphoreticular malignancies. • WAS is a life-threatening illness with severely reduced life expectancy. The majority of patients do not reach adulthood without disease-modifying intervention. • Over 400 unique mutations have been reported in the <i>WAS</i> gene, with severity correlating to the type of mutation and level of residual WASP expression. • Disease severity can be categorized using the Zhu score, a five-point scale based on clinical manifestations. Scores can change over time, with approximately 50% of patients progressing from mild to severe phenotype by age 30. • Main causes of death in patients with WAS are severe infections, hemorrhages, and malignancies. 	<ul style="list-style-type: none"> • WAS is a serious condition. The condition is life-threatening without disease-modifying intervention. • The severity of WAS is primarily determined by the specific <i>WAS</i> gene mutation, with disease progression often worsening over time.
Unmet Medical Need	<ul style="list-style-type: none"> • There is no FDA-approved treatment for WAS. • Allogeneic HSCT can be disease-stabilizing when successful, but carries significant risks and limitations: <ul style="list-style-type: none"> – Outcomes are less favorable for patients aged >5 years or with severe disease (Zhu score 5.0) – Best results are achieved with fully HLA-matched donors, which are not available for all patients – Complications are common, affecting about 50% of patients within the first year – Risks include graft failure, graft-versus-host disease, infections, and malignancies • Splenectomy, while potentially effective for thrombocytopenia, carries a significant long-term risk of bacterial sepsis and may not be effective for autoimmune thrombocytopenia. 	<ul style="list-style-type: none"> • For patients with severe WAS who have a mutation in the <i>WAS</i> gene and for whom no suitable HLA-matched related hematopoietic stem cell donor is available, there is a substantial unmet medical need. • Reduction in the rate of severe infections and moderate/severe bleeds are important treatment benefits for patients with WAS and their families.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	<ul style="list-style-type: none"> Two clinical studies in patients 0.98-12.4 years old were submitted. Expanded access data included patients 14 and 35 years old. The studies were open-label but used the patients' 12-month baseline medical history as a comparator to demonstrate reduction in the rate of severe infections and moderate/severe bleeds. The rate of severe infections decreased significantly from 2.001 infections per PYO in the 12 months before gene therapy to 0.155 infections per PYO in the 6-18 month period post-treatment. The rate of moderate and severe bleeding events decreased from 2.001 events per PYO in the 12 months before gene therapy to 0.797 events per PYO in the 0-12-month period post-treatment, and further to 0.028 events per PYO in the >4-year period. Platelet counts increased significantly and were sustained over time, with median counts rising from $18.00 \times 10^9/L$ at baseline to $59.00 \times 10^9/L$ at Year 1, and $84.00 \times 10^9/L$ at Year 5. All evaluable patients achieved cessation of sustained platelet infusions within 12 months post-treatment, with a median time to platelet transfusion independence of 49 days. Sustained engraftment of genetically corrected cells was observed in all patients, with adequate multilineage engraftment maintained in both bone marrow and peripheral blood cell populations. WASP expression in peripheral blood cells increased markedly after treatment and remained stable over time, reaching median values of 77.2% in platelets and 58.7% in lymphocytes by Day 180. T-cell function improved, with normalized proliferative responses to stimulation observed from 1 year post-treatment onwards. Eczema resolved or improved in all patients, with no patients having moderate or severe eczema from Year 1 onwards. The rate of hospitalizations decreased from 2.853 per PYO in the 12 months before gene therapy to 0.169 per PYO in the >6-month period post-treatment. Sustained immunoglobulin replacement therapy and antimicrobial treatment were discontinued in the majority of patients. 	<ul style="list-style-type: none"> Treatment with WASKYRA significantly reduced the rates of severe infections and moderate/severe bleeds, even after stopping sustained platelet infusions, immunoglobulin replacement therapy, and antimicrobials. Although the evaluable study population is small, the outcomes are markedly reduction compared to patients' baseline rates with potential durability as evidenced by the long follow-up periods in TIGET-WAS patients.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	<ul style="list-style-type: none"> Serious adverse events included device-related infections, febrile neutropenia, veno-occlusive liver disease, and thrombotic microangiopathy. These were generally related to conditioning or other study procedures rather than WASKYRA itself. The most common adverse events were infections (particularly upper respiratory tract infections), petechiae, pyrexia, diarrhea, vomiting, and eczema. Many of these occurred in the first 6 months post-treatment during immune reconstitution. One adult patient died due to deterioration of a pre-existing neurological condition about 4.5 months after treatment. This was considered unrelated to WASKYRA but relatedness to conditioning could not be excluded. One patient developed papillary thyroid cancer 5 years post-treatment. This was considered possibly related to conditioning and prior immunosuppression rather than WASKYRA. Insertional oncogenesis is a theoretical risk with lentiviral vectors. No evidence of this was observed, but longer follow-up in more patients is needed to fully assess this risk. Autoimmune/autoinflammatory events occurred but generally resolved post-treatment without immunosuppression in most patients. 	<ul style="list-style-type: none"> A postmarketing requirement to enroll a minimum of 40 patients in an observational, long-term study has been issued. This will provide additional information on the long-term risks of WASKYRA, including secondary malignancies.
Risk Management	<ul style="list-style-type: none"> The safety database was small and included only 28 patients. While no events of secondary malignancies were observed, this theoretic and serious risk that warrants continued surveillance. 	<ul style="list-style-type: none"> Risks associated with WASKYRA treatment and procedure can be mitigated with routine pharmacovigilance. The potential risk of insertional mutagenesis will be further investigated via a PMR safety study.

Abbreviations: HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; PYO, person-year of observation; WAS, Wiskott-Aldrich syndrome; WASP, Wiskott-Aldrich syndrome protein

11.2 Risk-Benefit Summary and Assessment

Wiskott-Aldrich syndrome is a rare, life-threatening, X-linked primary immunodeficiency and platelet disorder characterized by microthrombocytopenia, eczema, recurrent infections, and increased susceptibility to autoimmunity and malignancies. The disease significantly reduces life expectancy, with most patients failing to reach adulthood without disease-modifying intervention. Current treatment options are limited to supportive care and allogeneic HSCT, which carries significant risks and limitations, particularly for patients older than 5 years or those lacking a fully matched donor.

WASKYRA (etuvetidigene autotemcel) is an autologous, hematopoietic, stem cell-based GT that expresses the human WAS gene. After infusion, transduced CD34+ cells engraft in the BM, repopulate the hematopoietic compartment, and their progeny produce functional WASP protein. This approach aims to provide a long-term correction of the genetic defect without the risks associated with allogeneic HSCT.

Clinical data from 27 patients treated with WASKYRA across 2 studies and an EAP demonstrate a robust treatment effect over the follow-up period ranging from 1.19 to 13.26 years. Significant reductions were observed in the rates of severe infections and moderate to severe bleeding events. Platelet counts increased substantially and were sustained over time, leading to the cessation of platelet infusions in all evaluable patients. Sustained engraftment of genetically corrected cells was achieved in all patients, with marked increases in WASP expression across multiple cell lineages.

Importantly, clinical benefits were observed regardless of age at treatment, including in patients ≥ 5 years old, who typically have poorer outcomes with HSCT. Improvements were also noted in T-cell function, eczema resolution, and reduced hospitalization rates. The majority of patients were able to discontinue IgRT and sustained antimicrobial treatment.

The main risks associated with WASKYRA treatment are related to the conditioning regimen and the potential for insertional mutagenesis. However, no safety issues directly related to the GT product were reported, and no evidence of insertional oncogenesis has been observed to date.

Quantitative Benefit/Risk Assessment (qBRA) Consult

Dr. Xinyi Ng in the Office of Biostatistics and Pharmacovigilance, CBER provided qBRA consult which aligns with clinical team's benefit risk assessment (refer to Dr. Ng's review for details). Briefly, to contextualize the results of the clinical studies for WASKYRA with historical data from the literature regarding outcomes of hematopoietic stem cell transplantation (HSCT) using matched unrelated donor (MUD) as a comparator, a qBRA was conducted. This qBRA is meant as an exploratory analysis to facilitate and support clinical judgment of the benefits and risks and decision making associated with WASKYRA in comparison with HSCT (MUD) for the treatment of WAS. The qBRA decision model included 3 treatment benefits attributes (i.e., 5-year overall survival, infections post-treatment, and bleedings post-treatment) and 3 treatment-related risk attributes (i.e., acute graft versus host disease [GVHD], chronic GVHD and malignancies). Values for each benefit and risk attributes of WASKYRA and HSCT (MUD) were synthesized from the clinical studies, Applicant's submitted systematic

literature review and a targeted review of the existing literature conducted by the FDA benefit-risk reviewers. Differences between WASKYRA and HSCT (MUD) for each attribute were calculated and presented graphically.

Overall, compared to HSCT (MUD), WASKYRA has more favorable 5 year-OS and lower risk of GVHD; however, WASKYRA is less favorable in bleeding reduction. Infections post-treatment and the risk of malignancy are uncertain and depend on the input values. The benefit-risk trade-off requires clinical judgment, consideration of the therapeutic context (i.e., rare condition with limited therapeutic options), and the importance of avoiding GVHD versus avoiding malignancies as both are potentially fatal.

11.3 Discussion of Regulatory Options

The regulatory options were considered for patients 6 months to <24 months and those >24 months separately. There was strong evidence of clinical efficacy based on the reduction in the rate of moderate and severe bleeding and severe infections compared to patients' 12-month medical history baseline. The clinical efficacy was supported by sustained engraftment of genetically corrected cells in all patients, marked increases in WASP expression across multiple cell lineages, normalization of platelet counts with cessation of transfusion dependence, and restoration of T-cell function. Given the unmet medical need and lack of disease-modifying treatments for patients without available donors for HSCT, the treatment effect of WASKYRA overcomes the observed and theoretical risks. There is a favorable benefit-risk profile, and the clinical team supports traditional approval of WASKYRA for this patient population.

11.4 Recommendations on Regulatory Actions

The clinical review team recommends traditional approval for WASKYRA based on demonstration of safety and effectiveness.

11.5 Labeling Review and Recommendations

The review team made substantial recommendations to each section of the Prescribing Information based on analyses of the safety and efficacy data. Please see Table 18 below for a summary of significant changes to the United States Prescribing Information.

Table 18: Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indication and Usage	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	Indication was revised to "WASKYRA is indicated for the treatment of pediatric patients aged 6 months and older and adults with Wiskott-Aldrich Syndrome (WAS) who have a mutation in the WAS gene and for whom hematopoietic stem cell transplantation (HSCT) is appropriate and no suitable

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		human leukocyte antigen (HLA)-matched related stem cell donor is available
Section 2: Dosage and Administration	-	<p>Revised for brevity, to use active command language, and appropriate use of numerical bullets.</p> <p>Subsection on "Receipt" was added in section 2.3.</p> <p>Patient monitoring recommendation was added.</p>
Section 4: Contraindications	<ul style="list-style-type: none"> Hypersensitivity to the active substance or to any of the excipients Previous treatment with haematopoietic stem cell gene therapy. Contraindications to the mobilization and the conditioning regimen. 	<p>Revised to add previous HSCT treatment and appropriate cross-references.</p> <ul style="list-style-type: none"> Hypersensitivity to the active substance or to any of the excipients [see <i>Hypersensitivity and Infusion Related Reactions (5.1)</i>] Previous treatment with HSCT within 6 months prior to screening or HSCT with evidence of residual donor cells Previous treatment with hematopoietic stem cell gene therapy. Contraindications to the mobilisation and the conditioning regimen.
Section 5: Warnings and Precautions	<p>5.1 Central venous catheter (CVC) complications</p> <p>5.2 Hypersensitivity and infusion-related reactions</p>	Section 5.1 5.8, 5.9, 5.13 were deleted as it is not related the product or not appropriate as warning in section 5.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	5.3 Engraftment failure 5.4 Prolonged cytopenia 5.5 Transmission of an infectious agent 5.6 Thyroid disease 5.7 Risk of insertional oncogenesis 5.8 Autologous Use 5.9 Mobilisation, rituximab, and conditioning medicinal products 5.10 Interference with HIV testing 5.11 Blood, organ, tissue and cell donation 5.12 After WASKYRA Administration 5.13 Long-term follow-up	Additional section on serious infections was added based on adverse reactions reported in the clinical trials. Revisions were made overall to this section to appropriately describe the risk, and mitigation measures.
Section 6 Adverse Reactions (Safety)	-	The information in this section was revised based on the current labeling practice to describe WASKYRA exposure and safety database included in the USPI, for concise presentation of data and to remove redundant information. The list of adverse reactions was revised to comprehensively capture safety events occurring during the conditioning period and throughout the first year following WASKYRA administration.

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		A table with shift analysis of laboratory abnormalities was added.
Section 8.4: Pediatric Use	-	Revised to specify the data supporting the indication of WASKYRA in pediatric population.
Section 12: Clinical Pharmacology.	-	Revised to remove promotional language and to describe MOA supported by data.
Section 14: Clinical Studies	-	Section 14 was revised to describe the studies which provided the primary evidence of efficacy, intervention, population characteristics, and major efficacy results based on current labeling practice. Exploratory analyses were deleted as they are not informative.
Section 17: Patient Counseling Information	-	This section was revised for clarity, use of command language, and to include important risks listed in section 5 (Warning and Precautions).

Source: Created by FDA Associate Director for Labeling

11.6 Recommendations on Postmarketing Actions

The review team notes an important consideration for post-marketing surveillance: the first is the small Safety population and the continued monitoring for the incidence of secondary malignancies (a known risk of lentiviral GT products).

The clinical review team, the Division of Pharmacovigilance, and the Applicant mutually agreed upon the following clinical postmarketing requirements for this submission:

- A postmarketing, observational study of 40 patients, including 26 enrolled in the clinical studies, and 14 patients to be recruited from the Early Access Law or commercial treatment to assess and characterize the risk of secondary

malignancies and long-term safety following treatment with WASKYRA. The enrolled patients will be followed for 15 years after product administration. Milestone dates include:

- Final Protocol Submission: March 31, 2026
- Study Completion Date: September 30, 2026
- Final Study Report Submission: December 31, 2026