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Administration of OTL-103

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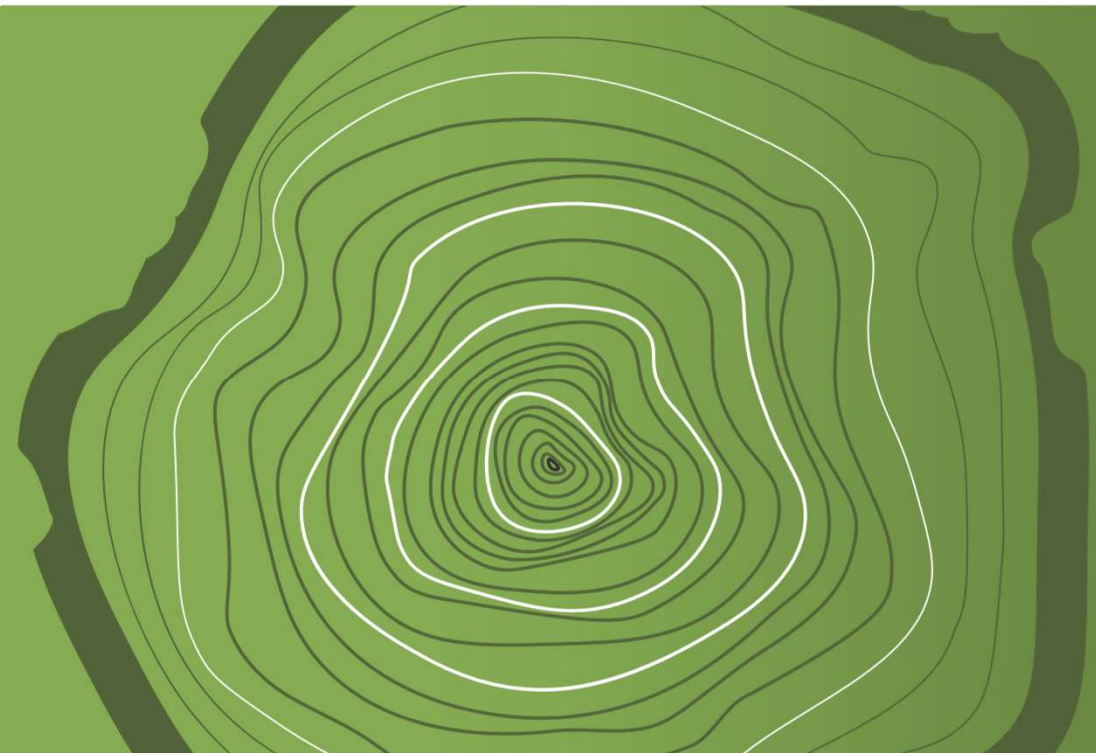

Rationale for new ICD-10 PCS code

- Current ICD-10-PCS codes do not adequately describe the Administration of the investigational therapy, OTL-103

- The new gene therapy approach used to design OTL-103 may be more specifically identified with an ICD-10-PCS procedure code that is unique to the product and the method of administration

Introduction of *ex vivo* autologous Hematopoietic Stem Cell gene therapy via intravenous (IV) infusion

- Providers may benefit by having a unique code to assist with tracking outcomes with OTL-103 therapy

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Wiskott-Aldrich Syndrome (WAS)

WAS accounts for 1.2% of all patients with identified primary immunodeficiencies (PID)[1]

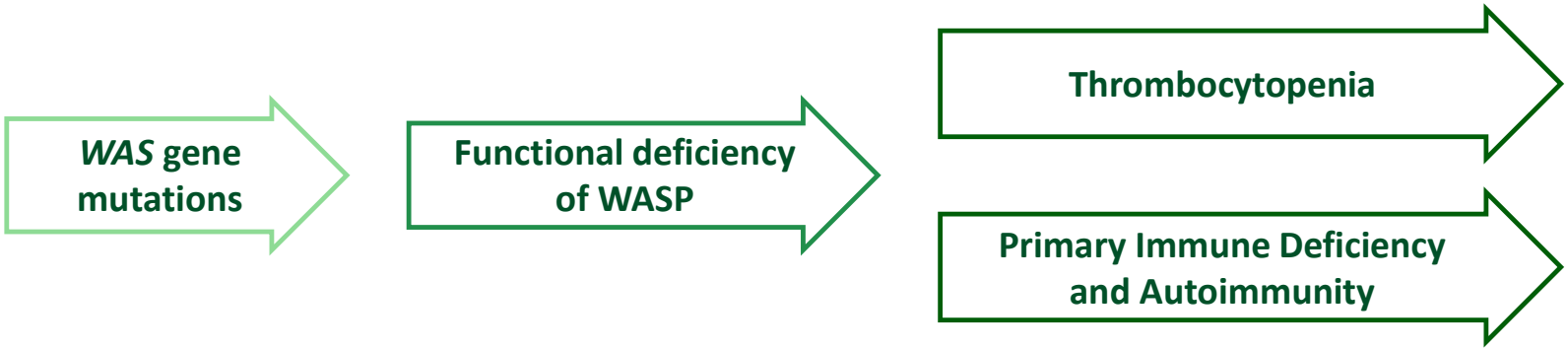
- It is a rare X-linked disorder caused by mutations in the *WAS* gene (located on the short arm of the X chromosome at Xp11.22 – p11.23) which encodes the WAS protein (WASP)[1-2]
- Mutations can lead to altered WASP expression and, therefore, altered function in non-erythroid hematopoietic cells[2]

Symptoms:

- WASP-deficient immune cells have compromised immunological synapse formation, cell migration, and cytotoxicity[3,4]
- WASP-deficient platelets have abnormal ultrastructure, function, and metabolic activity[5]
- WAS is characterized by symptoms that include recurrent or severe life-threatening infections, thrombocytopenia, and eczema[1] along with other manifestations including autoimmunity and malignancies[1]

Prognosis:

- Approximate survival is 15 years with supportive treatment[3]



1. Buchbinder D et al. Appl Clin Gen 2014;7:55–66; 2. Malik MA, Masab M. Wiskott-Aldrich Syndrome. [Updated 2019 Jun 22]. In: StatPearls [Internet]. Available at: https://www.ncbi.nlm.nih.gov/books/NBK539838 3. Ferrua F et al. Lancet 2019;6:e239–53; 4. Thrasher AJ, Burns SO. Nat Rev Immunol 2010;10:182-92. 5. Sereni L, et al. *J Allergy Clin Immunol* 2019;144(3):825-38.

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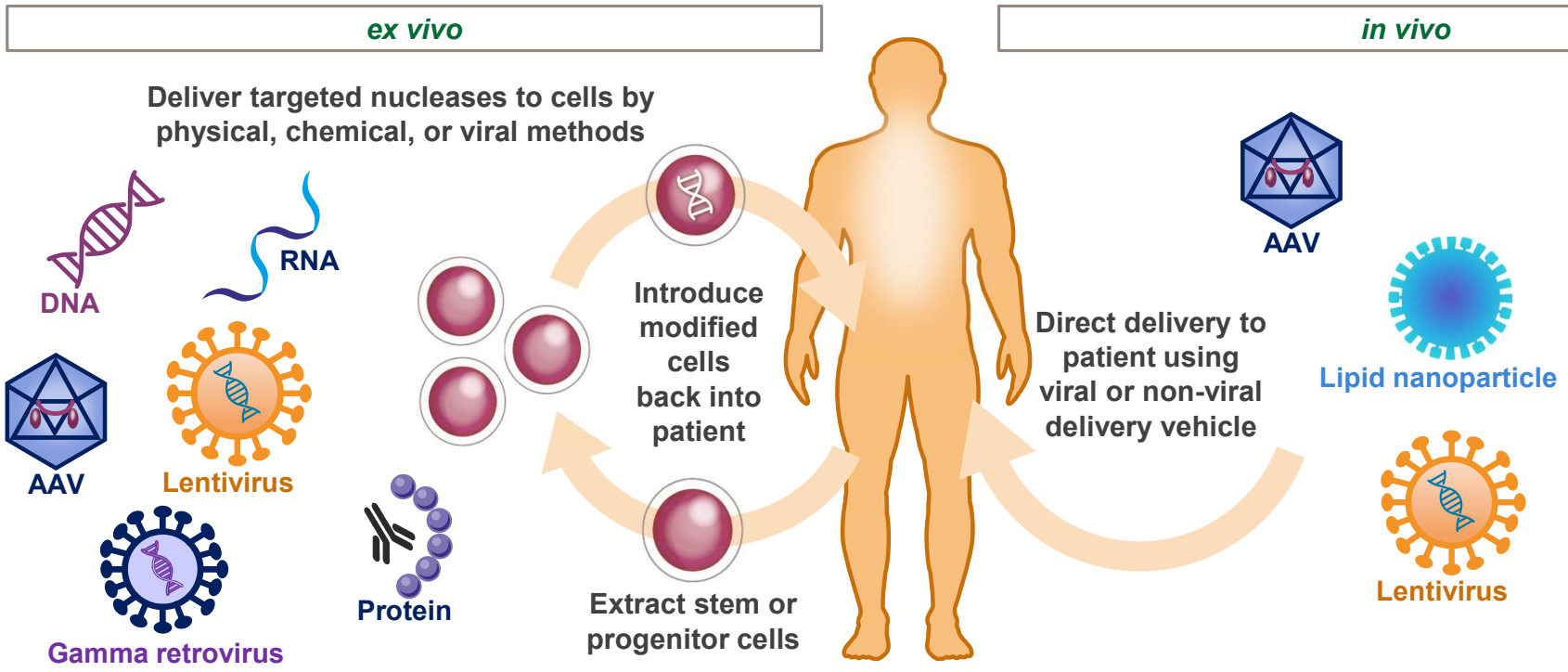
Different Gene Therapy Modalities Suited For Different Types Of Delivery Requirements And Diseases[1]



AAV, adeno-associated virus; DNA, deoxyribonucleic acid; HSC, hematopoietic stem cell; HSCT, hematopoietic stem cell transplant; RNA, ribonucleic acid.

1. Adapted from: FDA website. What is Gene Therapy? Available at: https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm573960.htm. Accessed February 14, 2019.
2. Kaufmann KB et al. *EMBO Mol Med*. 2013;5:1642–1661.

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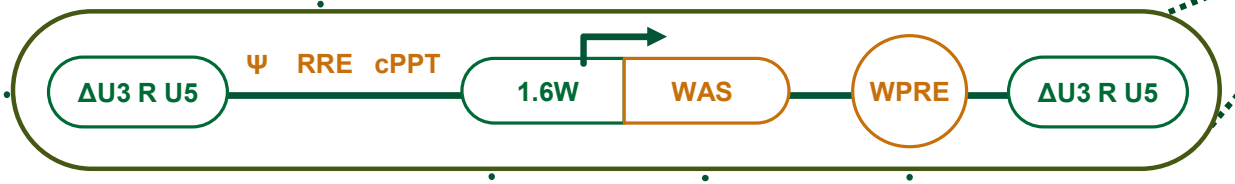
OTL-103 Investigational Therapy for WAS Utilizes a Lentiviral Vector to Introduce a Functional *WAS* Gene into Patient's HSPCs

Rev-responsive element (RRE)
Rev associates to the RRE, allowing WAS mRNA transcript export from the nucleus for translation into active protein

Lentiviral vector used to manufacture OTL-103 (LV-w1.6W WAS)

LV-w1.6W WAS

Lentiviral vector backbone with the SIN deletion (based on HIV-1)
Lentiviral vectors are capable of transducing dividing and non-dividing cells



1.6 kb Wiskott Aldrich Syndrome (*WAS*) promoter
Proximal endogenous *WAS* promoter. Drives expression in hematopoietic cells.

Human Codon-optimized *WAS* cDNA

Woodchuck hepatitis virus posttranscriptional regulatory element (WPRE)
WPRE is important for WAS mRNA transcript stabilization and increased WAS activity

OTL-103 consists of autologous CD34⁺ HSPCs genetically modified *ex vivo* by a self-inactivating LV vector encoding human *WAS* cDNA with expression driven by the endogenous *WAS* promoter leading to physiological expression in hematopoietic cells.

cPPT, central polypurine tract; GT, gene therapy; HSCPs, hematopoietic stem and progenitor cells; HIV-1, human immunodeficiency virus-1; LV, lentiviral; RNA, ribonucleic acid; RRE, rev-responsive element; SIN, self-inactivating; WAS, Wiskott-Aldrich syndrome; WPRE, Woodchuck hepatitis virus posttranscriptional regulatory element.

Aiuti A et al. Science 2013;341:1233151; Dupre L et al. Mol Ther 2004;105:903–14

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Ex vivo Autologous HSC Gene Therapy Investigational Approach

Patient returns home

Recovery:
Engraftment and reconstitution

Administration:
Genetically-modified cells (drug product) are infused into the patient intravenously

Conditioning:
Patient treated with a conditioning regimen to "make space" for the genetically-modified cells

Patient returns to center – Trip 2

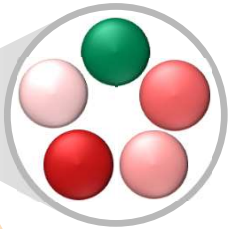
Cells shipped back to center

Cryopreserved genetically modified HSPCs:
Drug product must be certified that it meets manufacturing standards and sterility

Occurs at treatment center

Occurs at manufacturing location

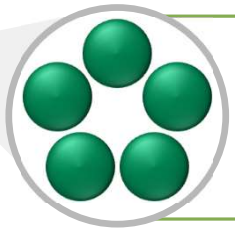
Patient enters center – Trip 1



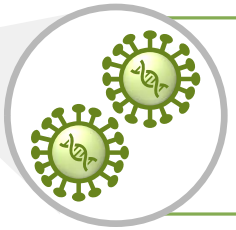
Blood cell collection:
Blood hematopoietic stem and progenitor cells (HSPCs) are taken from the patient via leukapheresis or bone marrow harvest

Patient returns home

Cells travel to manufacturing location



HSPC selection and purification:
HSPCs, identified by the CD34$^+$ cell surface marker, are selected and purified by magnetic bead selection



Transduction:
HSPCs are genetically modified outside of the body (*ex vivo*) via exposure to a viral vector carrying a functional copy of the missing or faulty gene

HSC: hematopoietic stem cell
HSPC: hematopoietic stem and progenitor cell

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Ex vivo Autologous HSC Gene Therapy Investigational Approach Anticipated Timeline

Outpatient monitoring:
- Local monitoring following procedure

Patient returns home

Recovery:
- Inpatient Observation
- Monitoring until cell count normalizes (varies by patient)

4-8 weeks

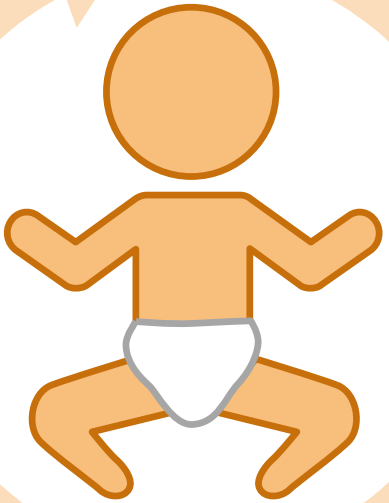
Administration:
- Infusion of drug product

1 day

Conditioning:
- Infusion of conditioning regimen
- Day of Rest

varies

Patient returns to center – Trip 2
Conditioning, Administration & Recovery



Manufacturing
- HSPC Selection and Purification
- Transduction
- QC and Cryopreservation

~10 days

Pre-collection activities:
- Patient eligibility per product labeling
- Cellular assessment

Patient enters center – Trip 1
Cell Collection

2-3 days

Bone marrow harvest:
- Admit patient day before harvest
- Perform the harvest
- Observe for 24 hours then discharge

OR

up to 7 days

Mobilized peripheral blood collection (leukapheresis):
- Pre-mobilization assessment
- Pre-treatment with mobilizing agents
- Possibility of 1-2 leukapheresis

Patient returns home

HSC: hematopoietic stem cell
HSPC: hematopoietic stem and progenitor cell

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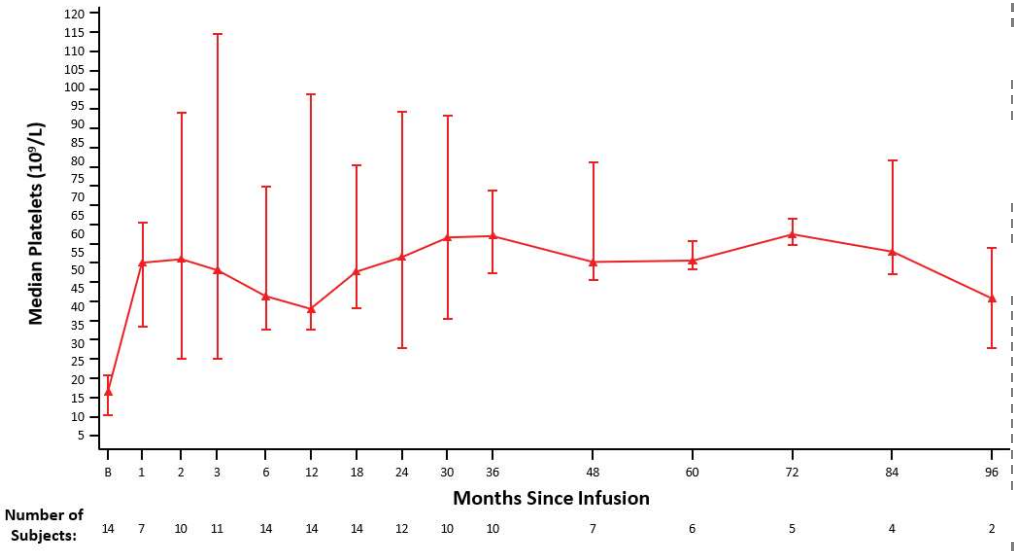
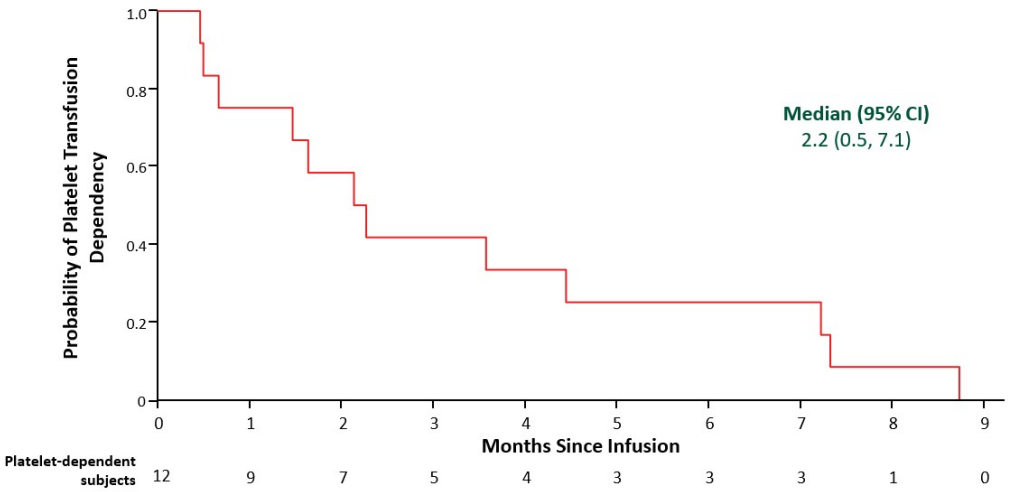
OTL-103 Investigational Therapy for WAS – Integrated Analysis: Platelets

Median (IQR) Platelet Count



IQR, interquartile range.
Baseline platelet values were calculated as the median of available values >7 days from a platelet transfusion prior to the treatment period, which began at mobilization. Platelet values within 7 days of a platelet transfusion were not included. When there were multiple platelet counts taken within one visit, a median platelet count for the subject's visit was calculated.

Time to Discontinuation of Platelet Transfusions



CI, confidence interval
Number of subjects still depending on platelet transfusion at the timepoint (transfusions related to adverse events were not included).
12 of the total 14 subjects are included in analysis as two subjects did not have post-treatment transfusions due to splenectomy.

Ferrua F, et al. Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy for Wiskott-Aldrich Syndrome (WAS): Up To 8 Years of Follow-up in 17 Subjects Treated Since 2010. Presented at the 61st American Society of Hematology (ASH) Annual Meeting, December 7-10, 2019. P3346.

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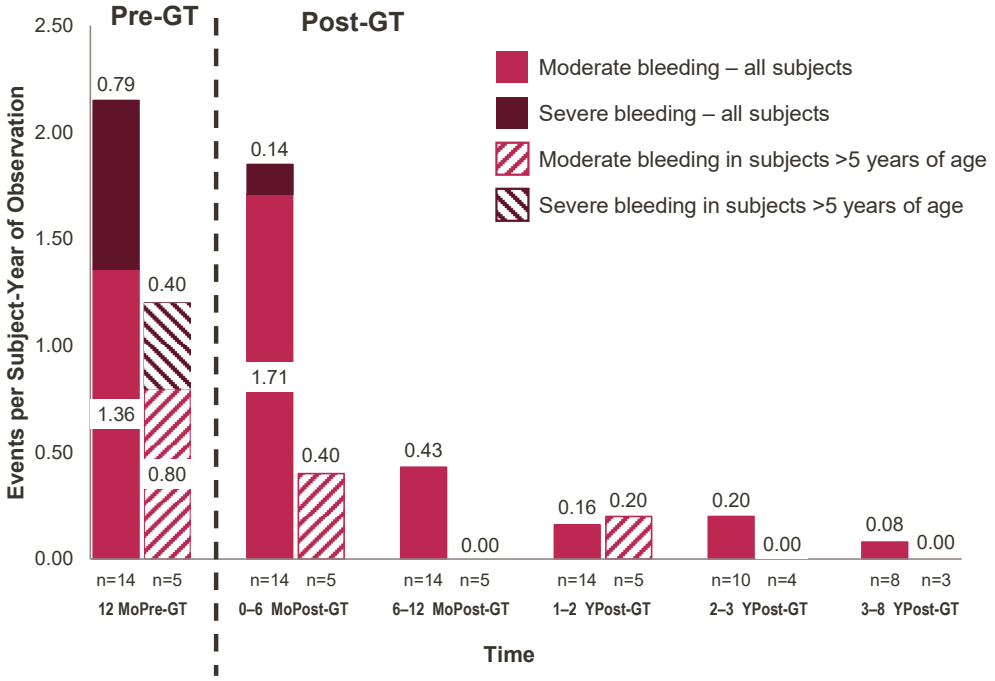
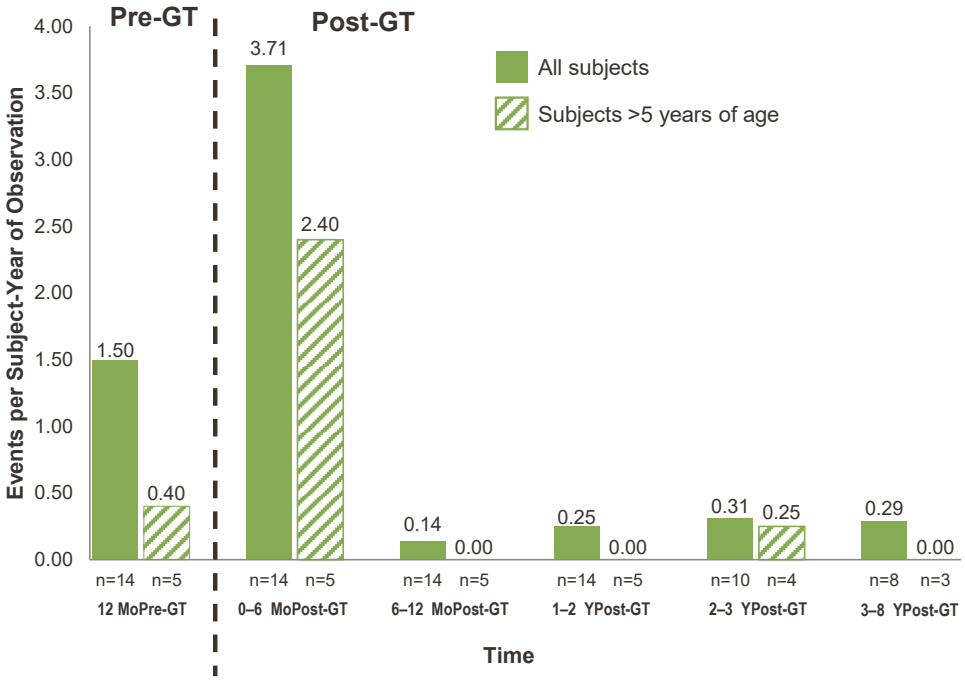
OTL-103 Investigational Therapy for WAS – Integrated Analysis: Bleeding and Severe Infections

Frequency and Severity of Bleeding Events



Severe Infections per Subject per Year



GT, gene therapy; mo, months; N, number of patients; Y, years.

Ferrua F, et al. Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy for Wiskott-Aldrich Syndrome (WAS): Up To 8 Years of Follow-up in 17 Subjects Treated Since 2010. Presented at the 61st American Society of Hematology (ASH) Annual Meeting, December 7-10, 2019. P3346.

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OTL-103 Investigational Therapy for WAS – Integrated Analysis: Clinical Summary

OTL-103 Therapy

- OTL-103 is an investigational *ex vivo* autologous HSC gene therapy that utilizes a lentiviral vector to insert a functional copy of the *WAS* gene into a patient's own $CD34^+$ HSPCs *ex vivo*, which are administered back into the patient
- OTL-103 proposed MOA is that genetically modified $CD34^+$ HSPCs engraft in the patient and are able to differentiate into functional cells, including lymphocytes and platelets, that express WASP

Safety Profile

- Most subjects experienced adverse events (AEs) related to the reduced-intensity conditioning regimen (mainly of mild or moderate grade).* No AEs related to OTL-103 have been reported to date as assessed by the investigator.
- There were 33 serious adverse events (SAEs) in 11 subjects pre-treatment, 23 SAEs in 10 subjects during the 0-6 months post-treatment period, and 3 SAEs in 3 subjects during the 6-12 month post-treatment period. No SAEs related to OTL-103 have been reported to date as assessed by the investigator.
- One EAP subject died 4.5 months post-treatment due to deterioration of an underlying neurodegenerative condition considered unrelated to OTL-103 by investigator

Efficacy Profile

- OTL-103 treatment showed: 1) sustained WASP expression in platelets, improved platelet counts, fewer and less severe bleeding events, and independence from platelet transfusions in all subjects, 2) sustained WASP expression in lymphocytes, a significant reduction in severe infection rate, and discontinuation of immunoglobulin supplementation in all subjects, suggesting reconstitution of immune function
- The integrated analysis of 17 subjects with up to 8 years' follow-up represents the largest data set and longest follow-up to date of subjects with WAS treated with gene therapy

* as assessed by the investigator

AEs, adverse events; EAP, expanded access program; HSCT, hematopoietic stem cell transplant; HSPC, hematopoietic stem and progenitor cell; MOA, mechanism of action; SAE, serious adverse event; WAS, Wiskott-Aldrich Syndrome; WASP, WAS protein.

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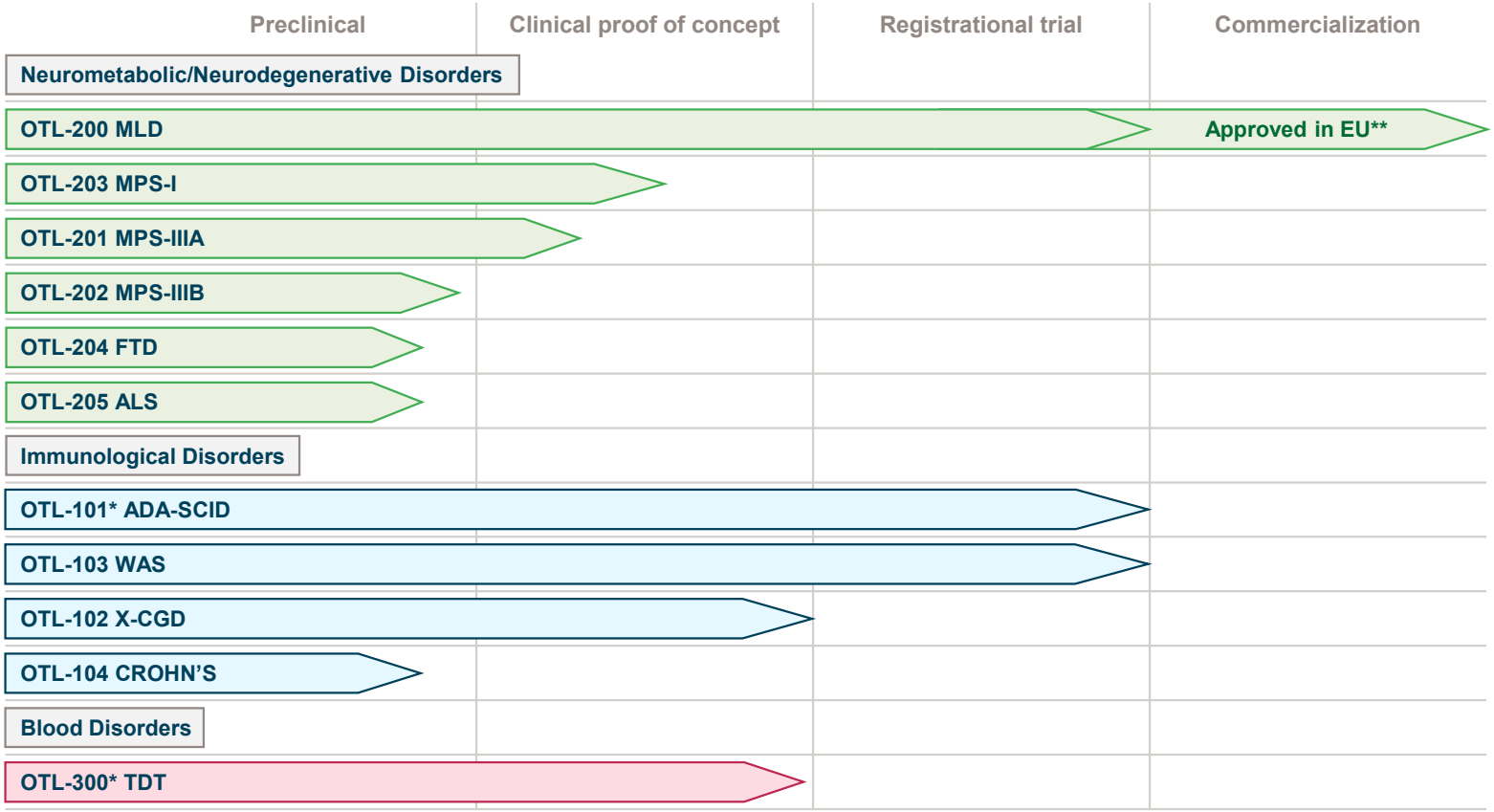
Orchard Pipeline



Several additional research and preclinical programs under development.

*New investments in this program are currently limited.

**Libmeldy™ (OTL-200) has been approved by the European Medicines Agency and has not been approved by the U.S. Food and Drug Administration or any other health authority. In the U.S., OTL-200 is an investigational therapy. All other therapies in our pipeline are investigational have not been approved by any regulatory agency or health authority.

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