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ex vivo Autologous Hematopoietic Stem Cell Gene Therapy

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March 8, 2022

Rationale for new ICD-10 PCS codes

- Current ICD-10-PCS codes do not uniquely describe the administration of the investigational therapies OTL-200 and OTL 103
- OTL-200 and OTL-103 will be better identified with ICD-10-PCS procedure codes that are specific to the products 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-200 and OTL-103 therapy

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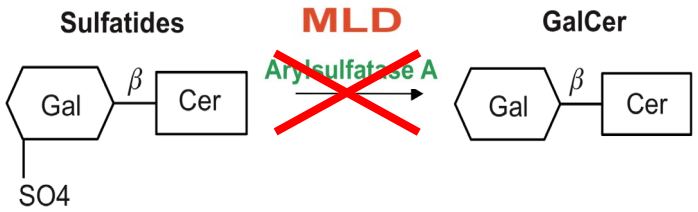
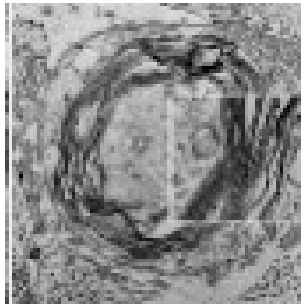
Metachromatic Leukodystrophy (MLD)

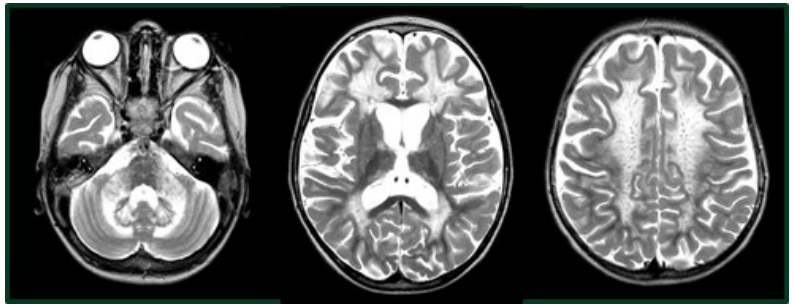
MLD
- a neurometabolic disorder that is one of the most common forms of leukodystrophy[1]
- It is a rare, autosomal recessive lysosomal storage disorder, caused by a deficiency of arylsulfatase A (ARSA) enzyme[1-5]

Symptoms, age of onset, and disease course vary
- All patients eventually experience severe motor impairment and neurological manifestations, including cognitive impairment[2]
- Prognosis is fatal: patients progress to dysphagia, decerebrated state, and death[1-2, 6-7]
- Disease progression is rapid for the majority of patients[7]

***ARSA* gene mutations** → **Functional deficiency of ARSA (lysosomal enzyme)** → **Intra-lysosomal sulfatide accumulation** → **Progressive demyelination & neurodegeneration**







ARSA, arylsulfatase A; MLD, metachromatic leukodystrophy.

1. Rosenberg JB et al. J Neurosci Res 2016;94(11):1169–79 2. Ferreira C et al. Translational Science of Rare Diseases 2 (2017) 1–71. 3. Gieselmann V, Krageloh-Mann I. Neuropediatrics 2010;41(1):1-6. 4. von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In:. The metabolic and molecular bases of inherited disease, Vol 3, 8th ed. McGraw Hill, 2001:3695,. 5. Gomez-Ospina N. Arylsulfatase A deficiency. In: GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018. . 6. Gieselmann V, Krageloh-Mann I. Neuropediatrics 2010;41(1):1–6. 7. Patil S, Maegawa GHB. Drug Des Devel Ther 2013; 7: 729–745.

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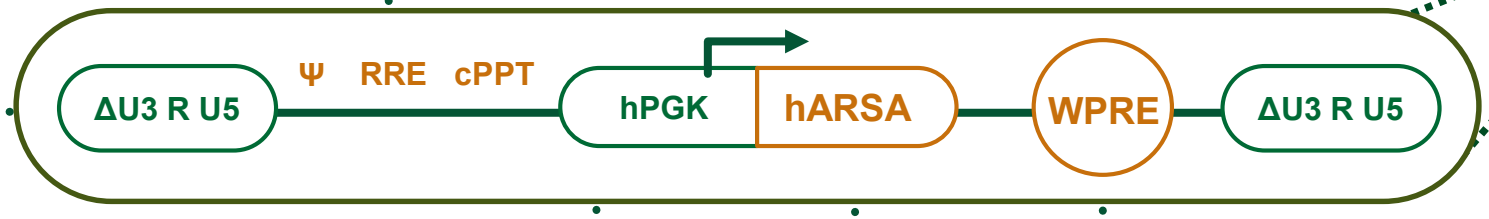
OTL-200 Investigational Therapy for MLD Utilizes a Lentiviral Vector to Introduce a Functional ARSA Gene into Patient's HSPCs

Rev-responsive element (RRE):
Rev associates to the RRE, allowing ARSA mRNA transcript export from the nucleus for translation into active protein[4]

Lentiviral vector used to manufacture OTL-200[3] (PGK.ARSA.LV)

PGK.ARSA.LV



Self-inactivating (SIN) Lentiviral Vector (LV) (based on HIV-1)
- SIN LVs have 400 bp deletion in U3 of the LTR inactivating the viral enhancer/promoter
- LV are capable of transducing dividing and non-dividing cells

PGK promoter
Cellular promoter lacking enhancers that could potentially transactivate proto-oncogenes near insertion site

Human ARSA cDNA

Woodchuck hepatitis virus post-transcriptional regulatory element (WPRE)
WPRE is important for ARSA mRNA transcript stabilization and increased ARSA activity

OTL-200 consists of autologous CD34⁺ HSPCs genetically modified *ex vivo* by a self-inactivating LV vector encoding for the human *ARSA* cDNA with constitutive expression driven by the human PGK promoter that can result in expression of ARSA in all blood cell progeny[1-3]

ARSA, arylsulfatase A; cPPT-CS, central polypurine tract-central termination sequence; HSCPs, hematopoietic stem and progenitor cells; LV, lentiviral vector; mRNA, messenger ribonucleic acid; PGK, phosphoglycerate kinase; WPRE, Woodchuck hepatitis virus post-transcriptional regulatory element; LTR, Long terminal repeat

1. Biffi A et al. Science 2013;341(6148):1233158. 2. Sessa M et al. Lancet 2016;388(10043):476-87. 3. Fumagalli F et al. Presented at: 16th Annual WORLD Symposium, February 10-13, 2020, Orlando, FL, USA 4. Brandt S et al. PLoS Pathog 2007;3(4):e54.

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GEN-USA-003

OTL-200 Investigational Therapy for MLD – Integrated Analysis: Clinical Summary

OTL-200 Therapy

- OTL-200 is an investigational *ex* vivo autologous HSC gene therapy that uses a lentiviral vector to insert a functional copy of the *ARSA* gene into a patient's own CD34+ HSPCs *ex vivo*, which are administered back to the patient
- OTL-200 proposed mechanism of action is that cells engraft into the patient, are able to cross the blood-brain barrier, differentiate into microglia, and provide cross-correction of nearby neurons and oligodendrocytes

Safety Profile

- The most commonly reported adverse events (AEs) potentially related to busulfan conditioning were febrile neutropenia, infections, liver disorders (including 3 VOD), stomatitis, and mucosal inflammation.* Five treatment-related AEs were reported in 4 patients (antibodies against ARSA), which resolved spontaneously or after treatment with rituximab, and with no obvious impact on pharmacodynamic effects, clinical outcomes, or overall safety profile.
- In patients treated with OTL-200 the most common serious adverse events (SAEs) associated with disease progression were motor dysfunction, dysphagia, muscle spasticity, seizure.** No SAEs or mortality related to OTL-200 have been reported to date.

Efficacy Profile

- All OTL-200 treated patients showed ARSA activity in CSF and peripheral blood within or above normal levels.
- OTL-200 treatment effects on ARSA enzymatic reconstitution of peripheral and central compartments, gross motor function, cognition, and other instrumental biomarkers shown to be durable up to 7.5 years post-treatment

ARSA, arylsulfatase A, CSF, cerebral spinal fluid; HSC, Hematopoietic Stem Cell; HSPC, hematopoietic stem and progenitor cell;
*These adverse events were not identified based on investigator's assessment but assigned retrospectively to busulfan, considering its known safety profile in relation to the nature, frequency and severity of reported adverse events. ** Symptoms of MLD (not predefined) were reported only if clinically significant and NCI CTCAE Grade ≥3. AEs were manually reviewed by the Sponsor and confirmed by the investigators after database lock to identify AEs typically associated with symptoms of MLD (e.g., ataxia, motor impairment, muscle spasticity, dysphagia). The decision to classify an event as associated with MLD was based on clinical judgement and experience with MLD

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Wiskott-Aldrich Syndrome (WAS)

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

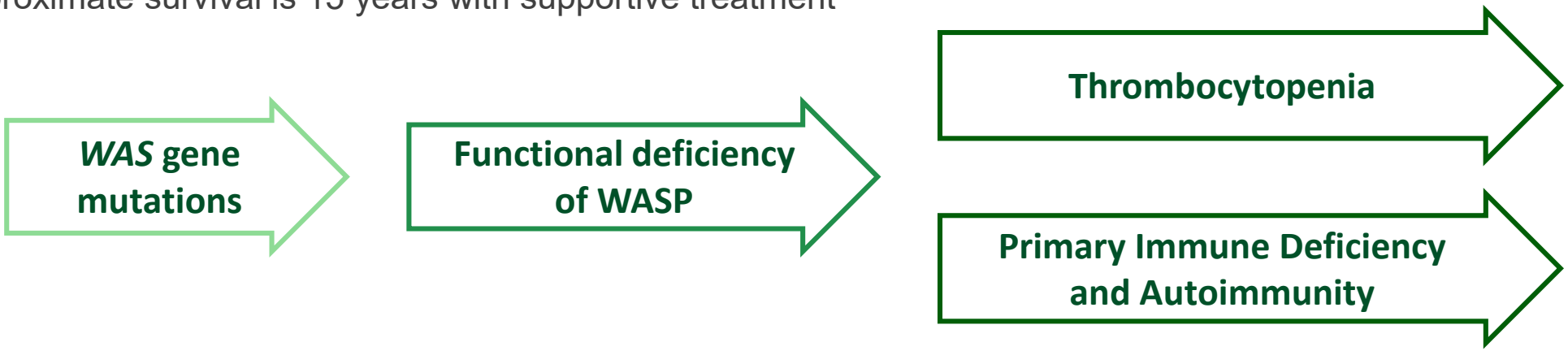
- It is a rare X-linked disorder caused by mutations in the *WAS* gene (located on the short arm of the X chromosome at Xp11.22 – p11.23) which encodes the WAS protein (WASP)[1-2]
- Mutations can lead to altered WASP expression and, therefore, altered function in non-erythroid hematopoietic cells[2]

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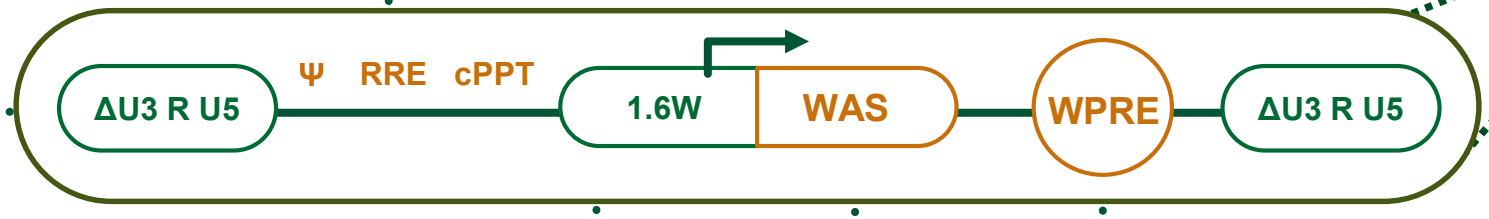
OTL-103 Investigational Therapy for WAS Utilizes a Lentiviral Vector to Introduce a Functional *WAS* Gene into Patient's HSPCs

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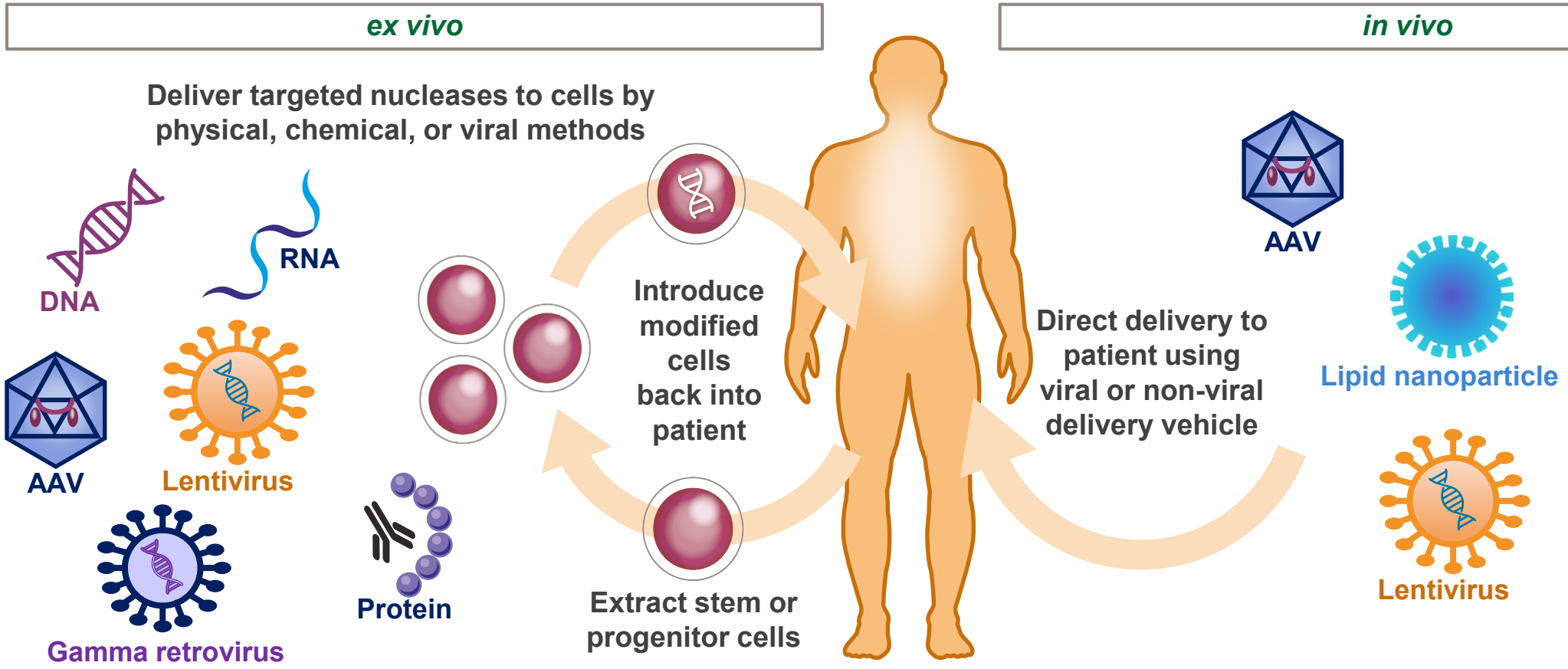
Different Gene Therapy Modalities Suited For Different Types Of Delivery Requirements And Diseases[1]



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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Ex vivo Autologous HSC Gene Therapy Investigational Approach

Patient returns home

Recovery:
Engraftment and reconstitution

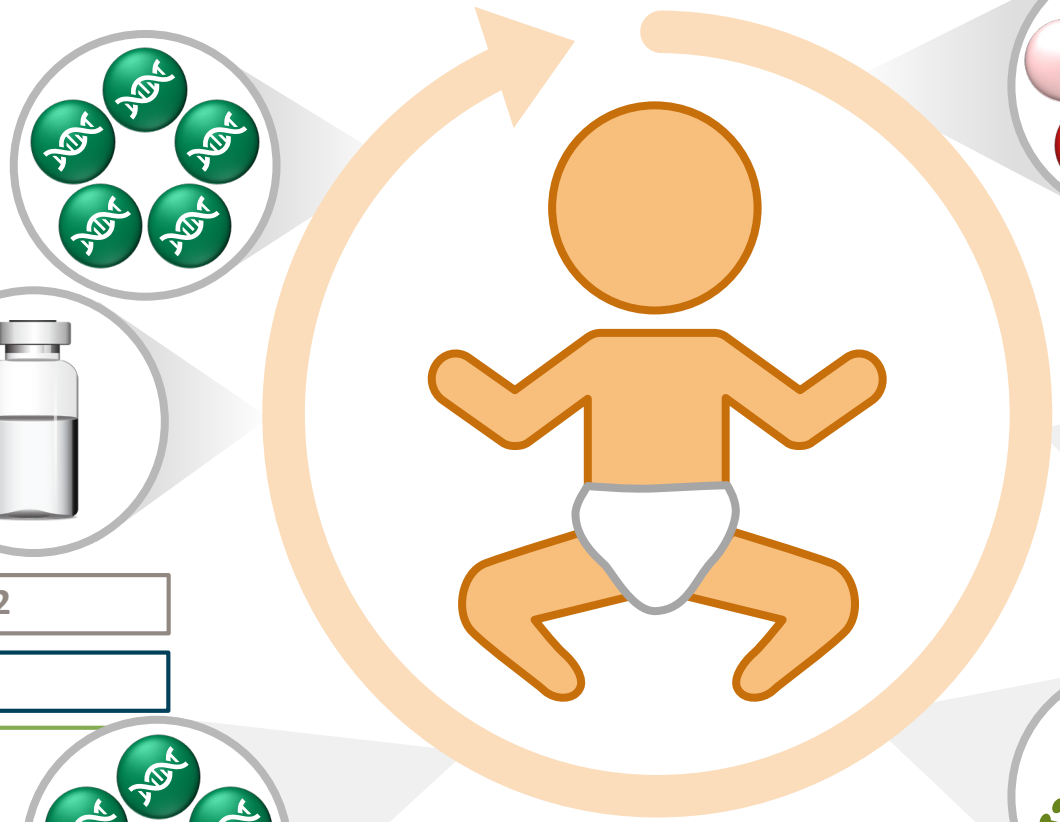
Administration:
Genetically-modified cells (drug product) are infused into the patient intravenously

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



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

Occurs at treatment center

Occurs at manufacturing location

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

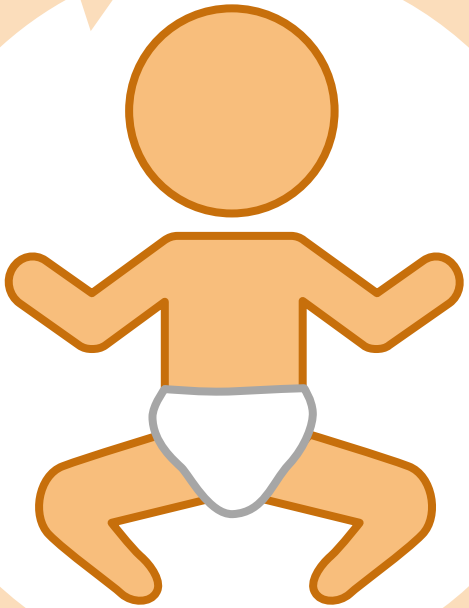
Administration:
- Infusion of drug product

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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