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Administration of OTL-200

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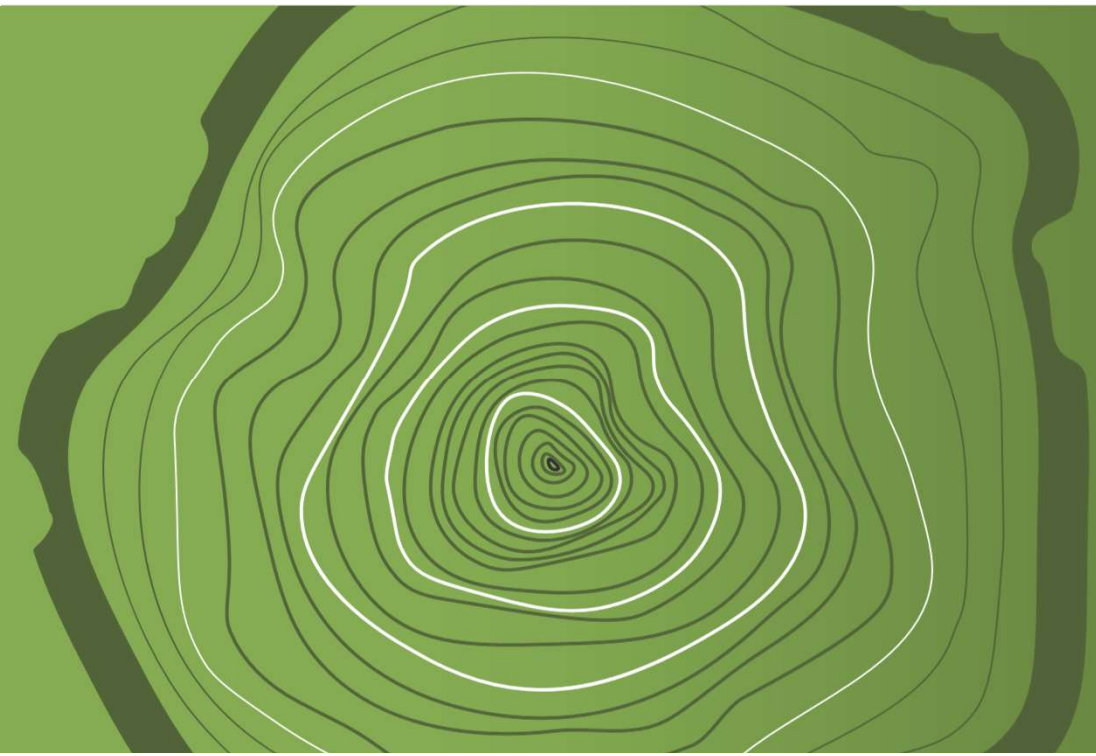

Rationale for new ICD-10 PCS code

- Current ICD-10-PCS codes do not adequately describe the Administration of the investigational therapy, OTL-200

- The new gene therapy approach used to design OTL-200 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-200 therapy

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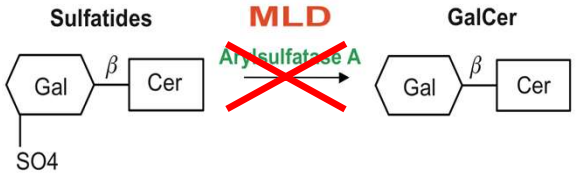
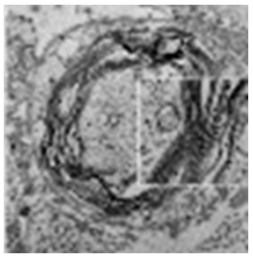
Metachromatic Leukodystrophy (MLD)

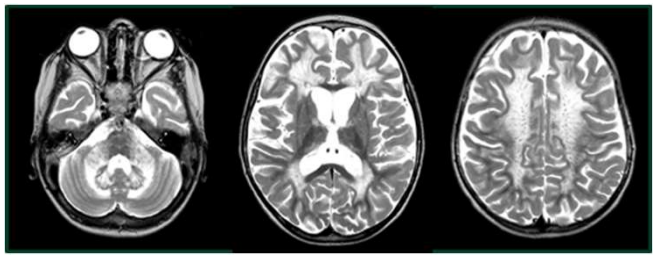
MLD
- a neurometabolic disorder that is one of the most common forms of leukodystrophy[1]
- It is a rare, autosomal recessive lysosomal storage disorder, caused by a deficiency of arylsulfatase A (ARSA) enzyme[1-5]

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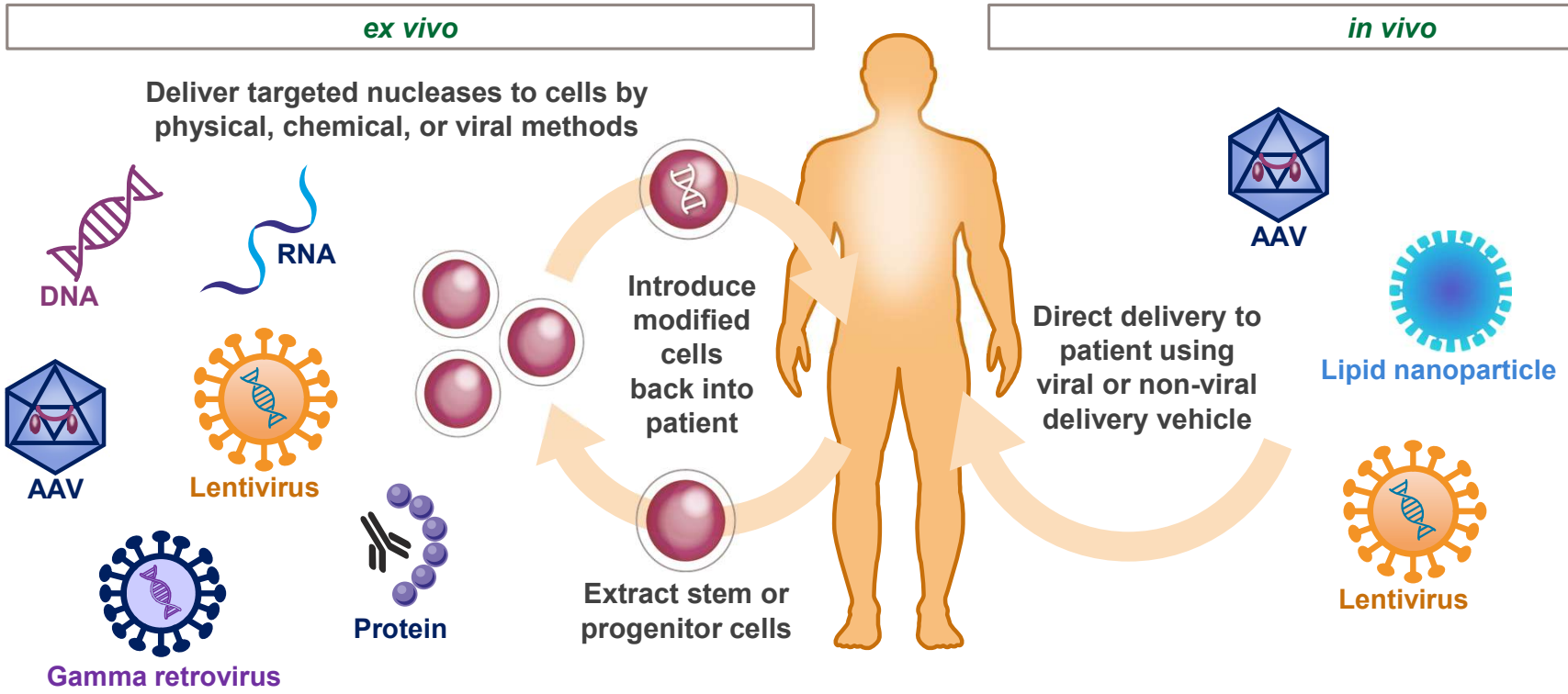
Different Gene Therapy Modalities Suited For Different Types Of Delivery Requirements And Diseases[1]



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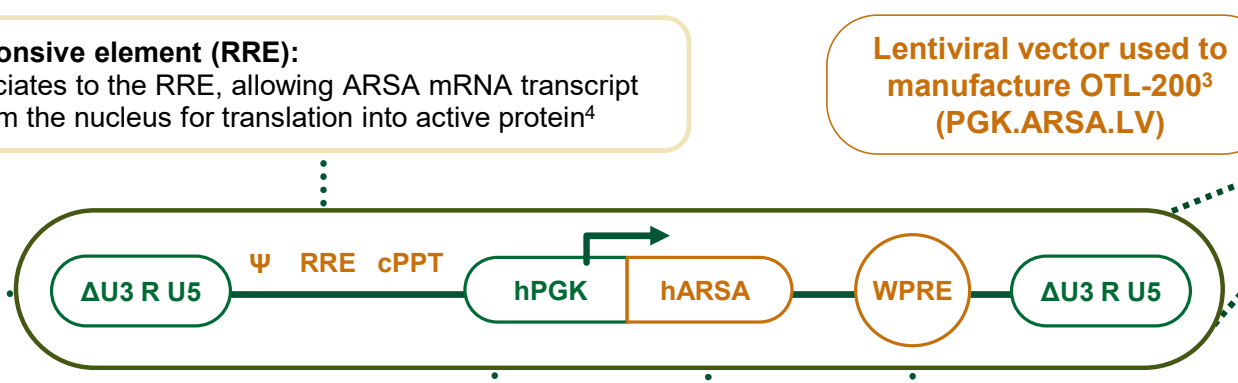
OTL-200 Investigational Therapy for MLD Utilizes a Lentiviral Vector to Introduce a Functional ARSA Gene into Patient's HSPCs

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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Ex vivo Autologous HSC Gene Therapy Investigational Approach

Patient returns home

Recovery:
Engraftment and reconstitution

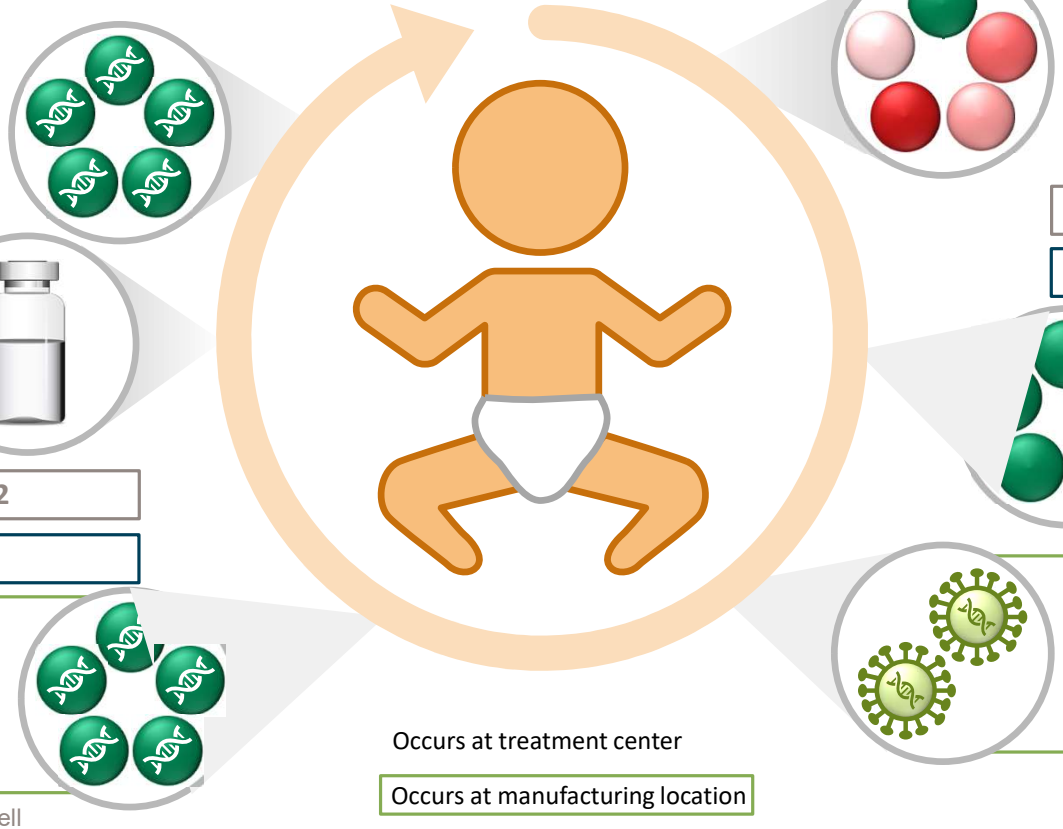
Administration:
Genetically-modified cells (drug product) are infused into the patient intravenously

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

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

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

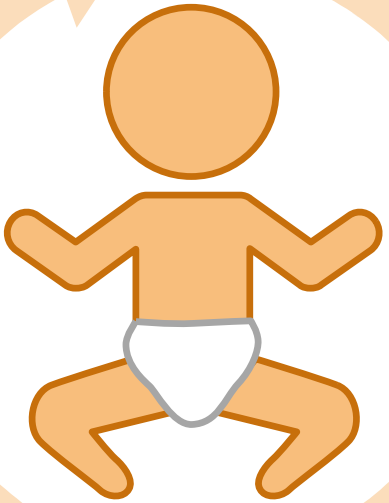
Administration:
- Infusion of drug product

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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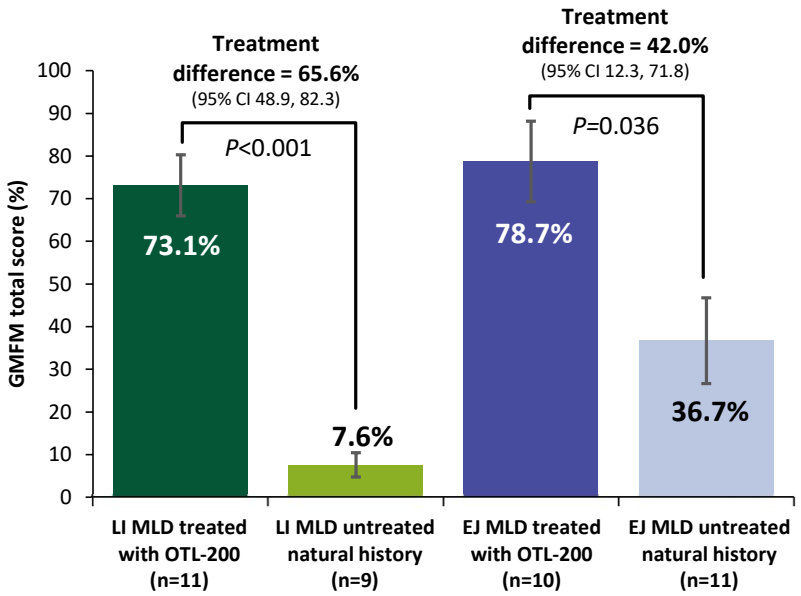
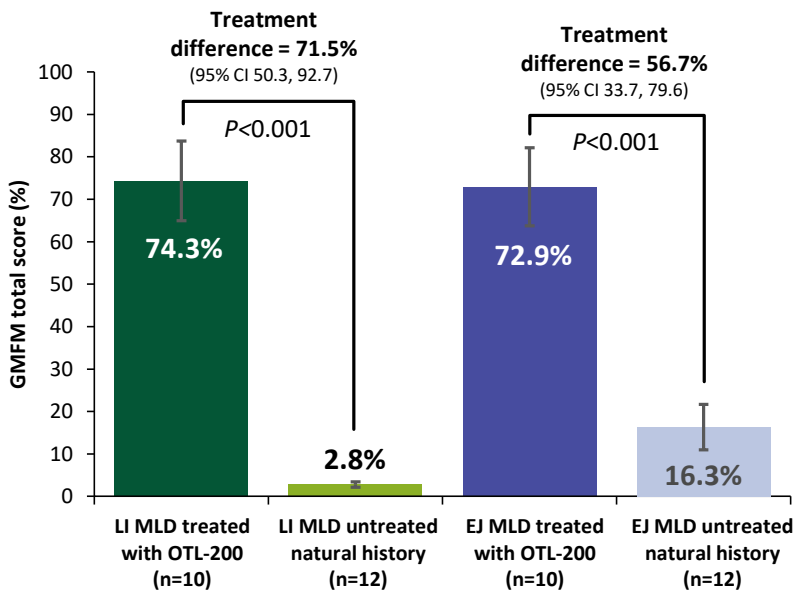
OTL-200 Investigational Therapy for MLD – Integrated Analysis: Gross Motor Function Measure (GMFM)

OTL-200 vs. Natural History

Year 2 (Co-primary endpoint)



Year 3



Note: vertical error bars are standard error of the mean

CI, confidence interval; EJ, early juvenile; GMFM, gross motor function measurement; GT, gene therapy; HSC, hematopoietic stem cell; LI, late infantile; MLD, metachromatic leukodystrophy.Figure from Fumagalli F et al. Lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit; Presented at: 2019 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); September 3-6, 2019; Rotterdam, The Netherlands

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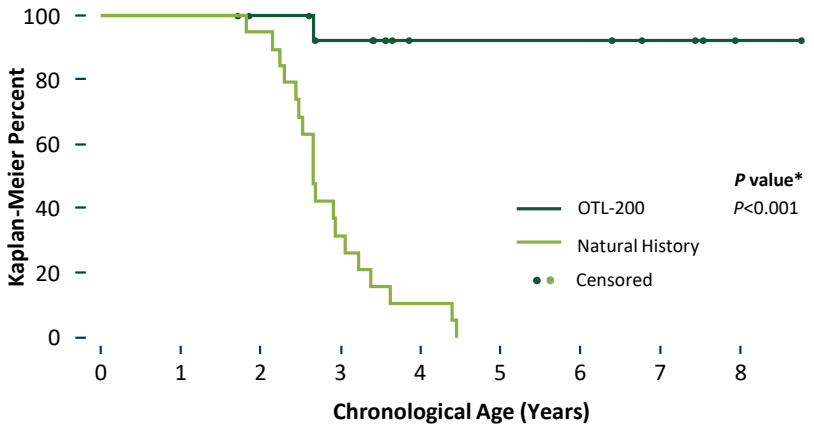
OTL-200 Investigational Therapy for MLD – Integrated Analysis: Severe Motor Impairment Free Survival (sMFS)

Late Infantile

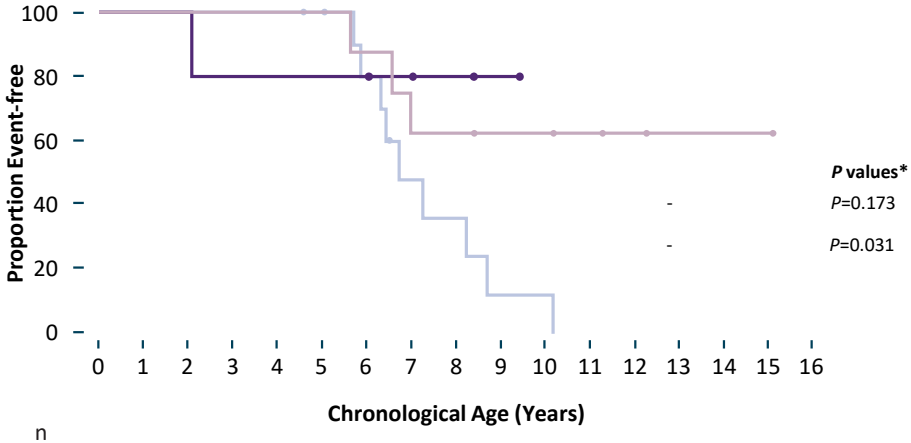
OTL-200 vs. Natural History



n										
OTL-200	16	16	14	11	6	6	6	4	1	0
Natural History	19	19	18	6	2	0	0	0	0	0

Early Juvenile

OTL-200 by Symptomatic Status vs. Natural History



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OTL-200 EJ Psymp	5	5	5	4	4	4	4	3	2	1	0	0	0	0	0	0	0
OTL-200 EJ Symp	8	8	8	8	8	8	7	5	5	4	4	3	2	1	1	1	0
Natural History	12	12	12	12	12	11	8	4	3	1	1	0	0	0	0	0	0

*P-values calculated using an unstratified log-rank test

Severe motor impairment free survival (sMFS) is defined as the interval from birth to the earlier of loss of locomotion and sitting without support (GMFC level 5 or higher) or death from any cause; otherwise sMFS is censored at the last GMFC assessment date. Natural history patients also presented. Figure from Fumagalli F et al. Lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit; Presented at: 2019 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); September 3-6, 2019; Rotterdam, The Netherlands7

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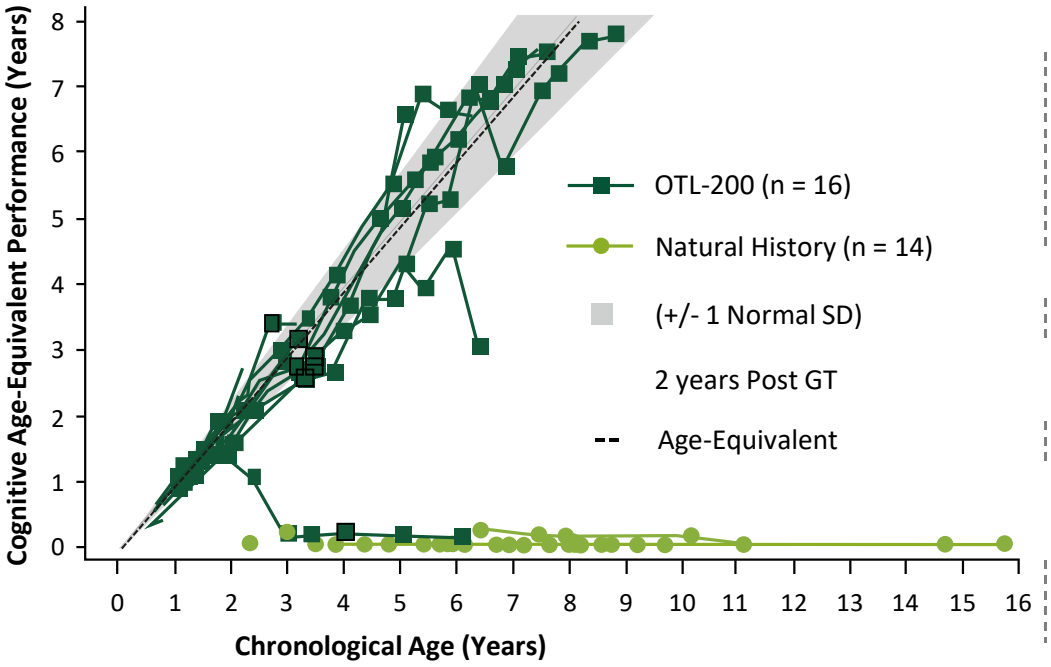
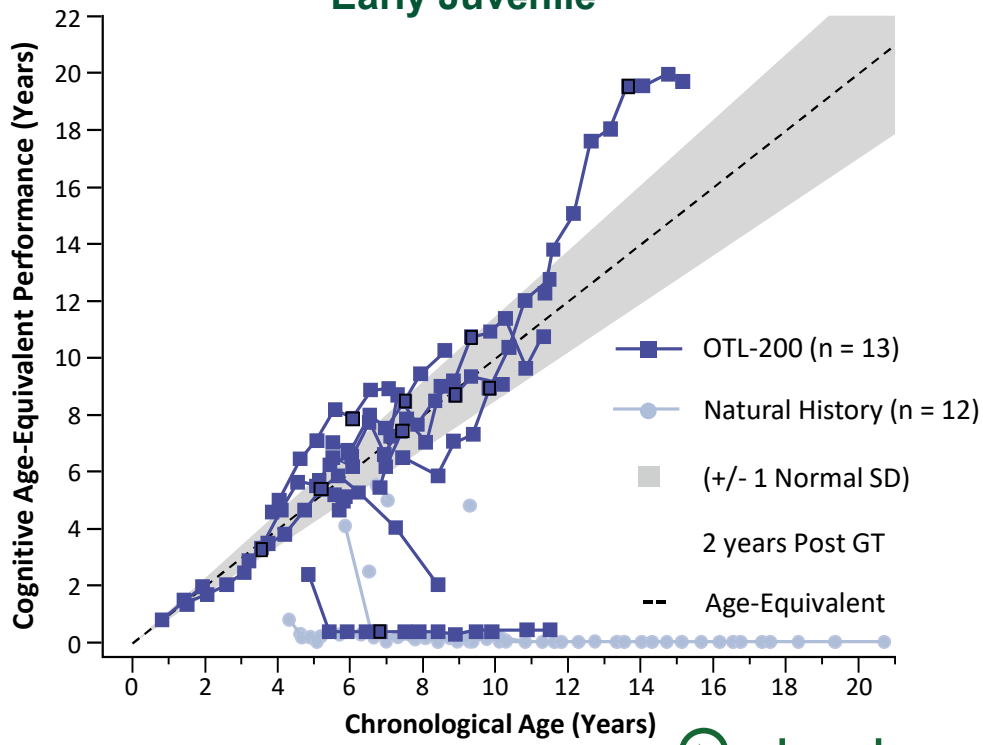
OTL-200 Investigational Therapy for MLD – Integrated Analysis: Cognitive Age-Equivalent (Performance)

OTL-200 vs. Natural history

Late Infantile



Early Juvenile



GT, gene therapy; SD, standard deviation.

Figures from Fumagalli F et al. Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy (HSPC-GT) for Metachromatic Leukodystrophy (MLD): Clinical Outcomes from 33 Patients Presented at: 16th Annual WORLDSymposium, February 10-13, 2020, Orlando, FL, USA

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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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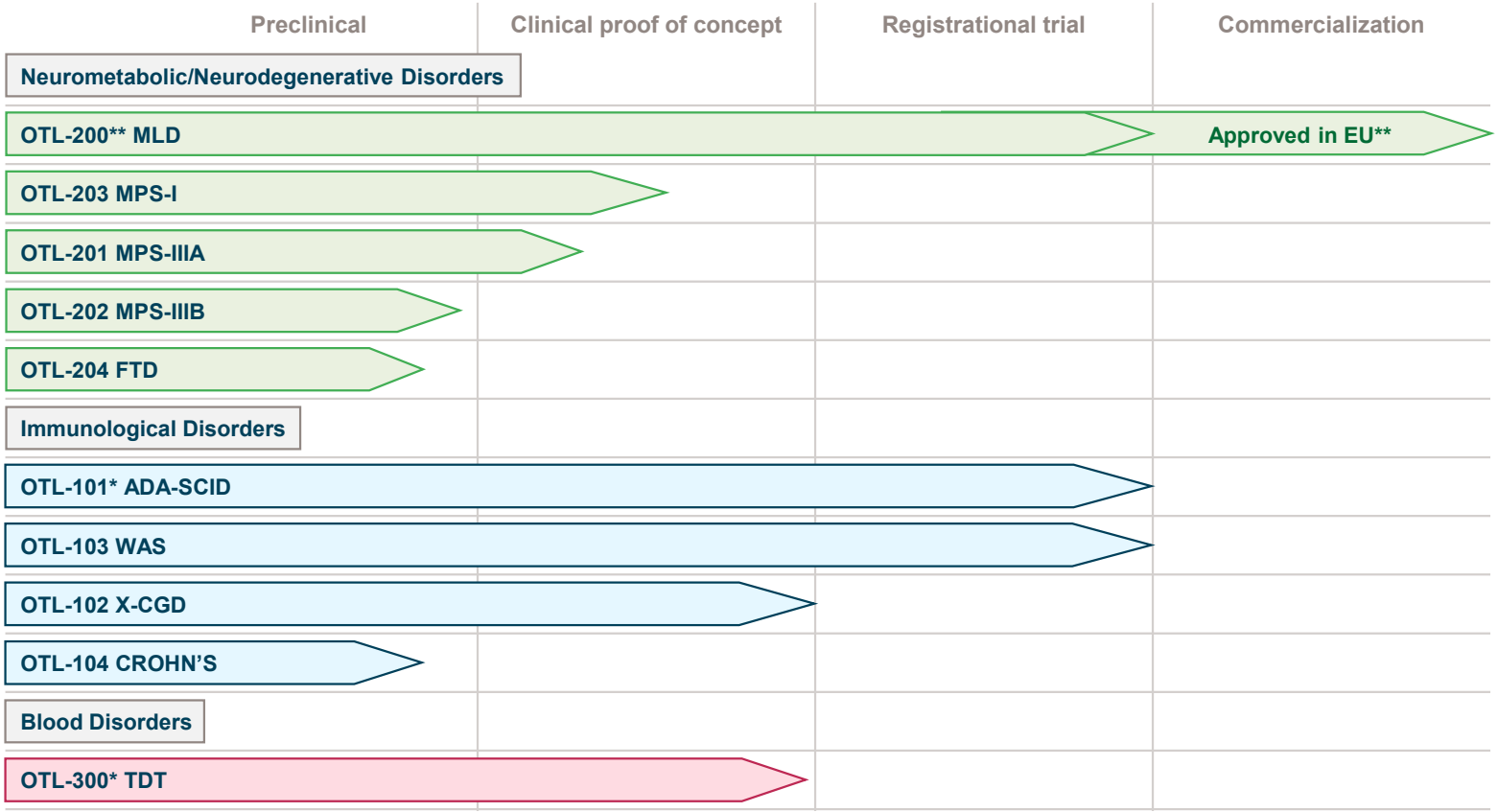
Orchard Pipeline



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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