We aspire to end the devastation caused by genetic and other severe diseases through the curative potential of HSC gene therapy.

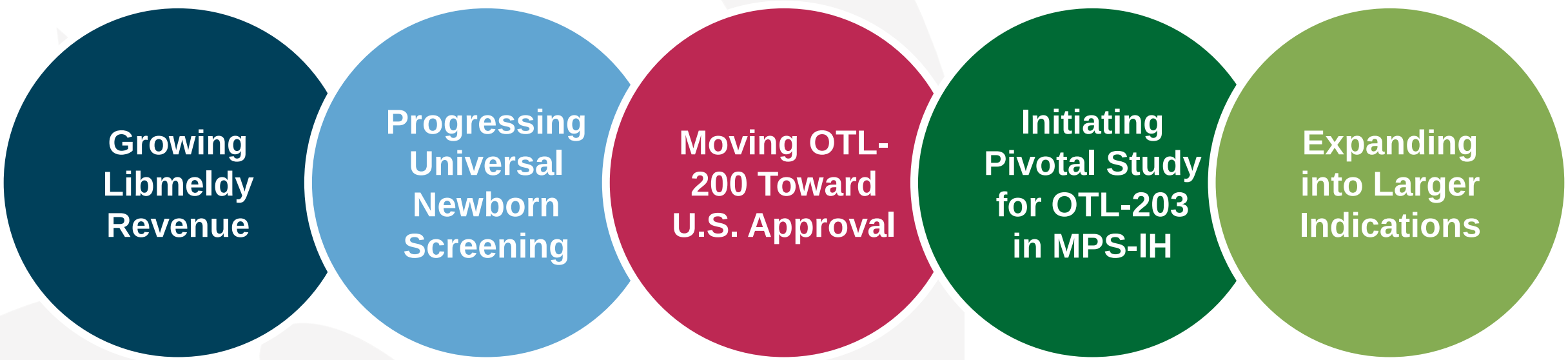
Forward-looking Statements

This presentation and statements made in this presentation contain forward-looking statements, which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements may also be identified by words such as “anticipates,” “potential,” “expects” and other similar expressions. Forward-looking statements include express or implied statements relating to, among other things: Orchard’s estimates and expectations with respect to its financial performance, including revenue, expenses, trend of cash-burn rates and cash-runway; the incidence rate of diseases that our products and product candidates are intended to treat, including the incidence of MLD; the therapeutic potential of Orchard’s products and product candidates, including the ability of HSC gene therapy to address larger indications; Orchard’s expectations regarding the timing of regulatory submissions and approvals of its product candidates, including the timeline for acceptance of Orchard’s BLA submission for OTL-200; Orchard’s expectations regarding the timing of U.S. approval for OTL-200; the additional proceeds receivable by Orchard upon exercise of the warrants issued pursuant to its previously announced strategic financing; the number of newborns expected to be screened for MLD, and the timing and likelihood of additional newborn screening studies; and Orchard’s ability and expectations to meet its anticipated 2023 milestones, as further described in this release.

These statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, many of which are beyond Orchard’s control, which could cause actual results to differ materially from those contemplated in these forward-looking statements. In particular, these risks and uncertainties include, without limitation: Orchard’s anticipated cash runway assumes U.S. FDA approval of OTL-200 in the first half of 2024, which may be delayed or not occur, and achievement of net sales in the U.S. and Europe in line with management’s forecasts, which may not happen; the risk that Orchard’s OTL-200 BLA submission is not accepted on the timeline we expect or at all; the risk that our revenues will be less than we anticipate; the risk that our expenses will be greater than we anticipate; the risk that Orchard is unable to set up additional qualified treatment centers and newborn screening or is delayed in doing so; the risk that Orchard will not maintain marketing approval; the risk that long-term adverse safety findings may be discovered; the risk that the warrants issued pursuant to Orchard’s previously announced strategic financing are not exercised, that only a subset of the warrants are exercised, or that the exercise price of the warrants is lower than anticipated due to a delay in OTL-200’s U.S. approval. Given these uncertainties, the reader is advised not to place any undue reliance on such forward-looking statements. Other risks and uncertainties faced by Orchard include those identified under the heading "Risk Factors" in Orchard’s most recent annual or quarterly report filed with the SEC, as well as subsequent filings and reports filed with the SEC. The forward-looking statements contained in this press release reflect Orchard’s views as of the date hereof, and Orchard does not assume and specifically disclaims any obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

Orchard therapeutics

Strong Operational Execution in 1H of 2023



Q2'23: Highest quarterly sales to date; Cumulative net sales of $25.9M

Four cases of MLD identified following ~150k newborns screened

BLA submission completed; potential approval in 1H'24

Global RCT in 40 patients following IND clearance by FDA

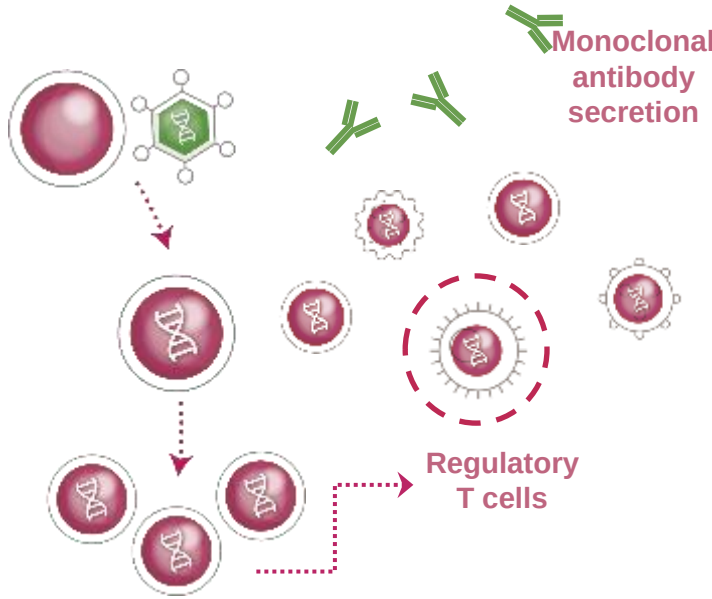
Preclinical PoC data in GRN-FTD and NOD2-Crohn's presented at ASGCT

Strategic financing resulted in $68M of new capital, extending cash runway into mid-2025

Potential for up to an additional $120M in proceeds could further offset financing needs for foreseeable future

Orchard therapeutics

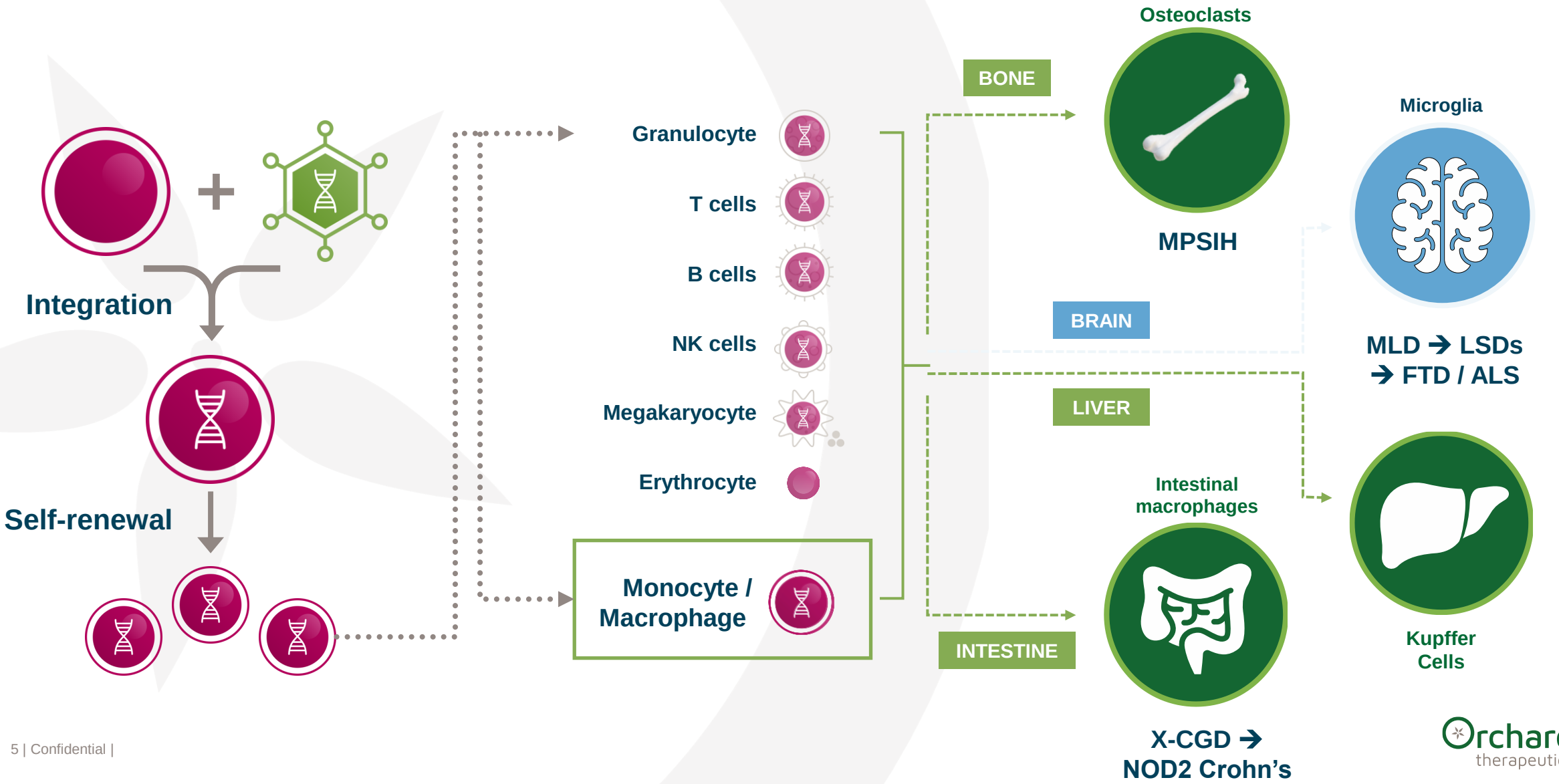
Orchard's HSC Gene Therapy Offers a Highly Differentiated, Validated Approach with Opportunities for Expansion

Validation in Rare Diseases	Larger Indications	Future Applications
libmeldy® (atidarsagene autotemcel)	OTL-104 NOD2-Crohn's	
OTL-200 MLD (US)	OTL-204 FTD	
OTL-203 MPS-I OTL-201 MPS-IIIA	OTL-105 HAE	
Other undisclosed programs		

Multiple opportunities for near-term data and inflection points through internal investment and business development

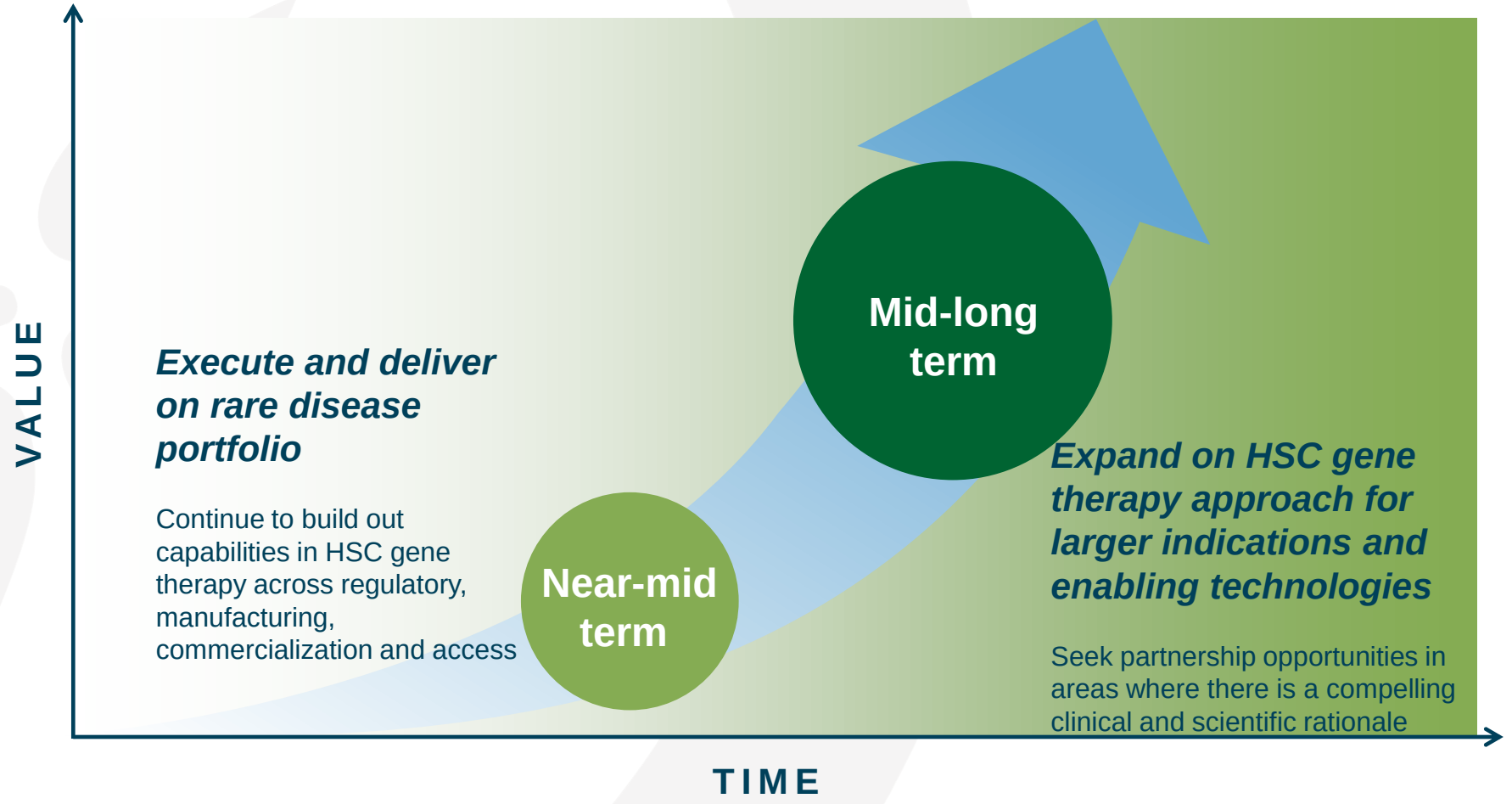
Orchard therapeutics

HSC Gene Therapy Allows Delivery of Gene-corrected Cells to Multiple Organ Systems



Orchard therapeutics

Strategic Long-term Growth and Value Creation with Expansion into Larger Indications



Orchard therapeutics

OTL-200 (MLD): Potential Significant Clinical Benefit for a Devastating Genetic Disease

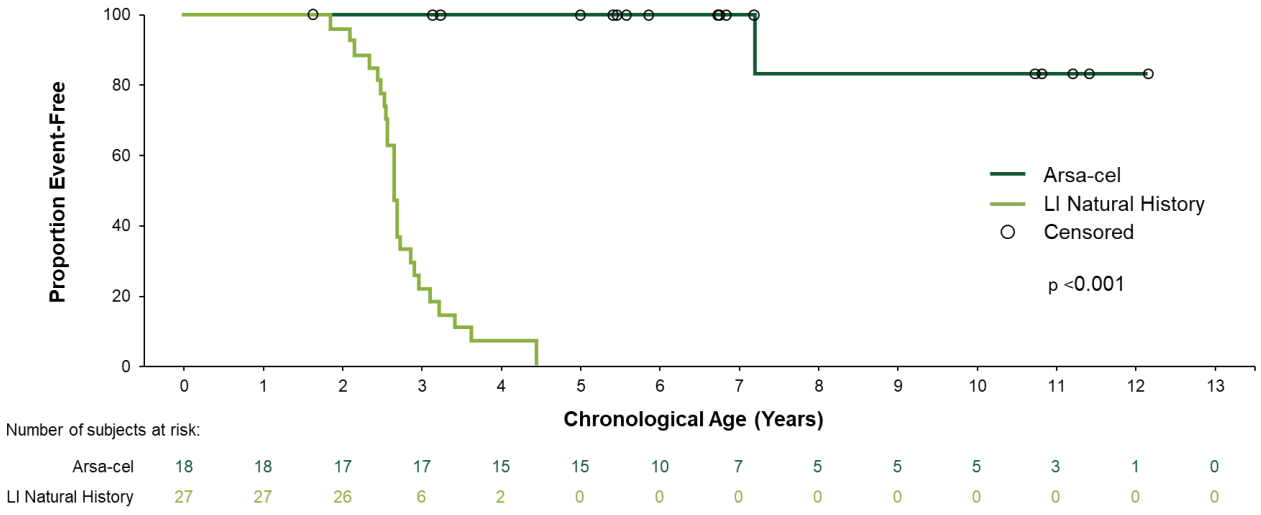
Age 5, pre-diagnosis

Age 9, advanced disease

Disease Snapshot

- Fatal genetic CNS disorder
- Rapid and irreversible loss of motor and cognitive function
- In its most severe form, most children pass away within five years of symptom onset[1]

Kaplan-Meier Plot of Severe Motor Impairment-Free Survival Pre-Symptomatic Late Infantile Subjects (n=18)



Data presented at 19th Annual WORLD*Symposium*™, February 2023

GMFC-MLD=Gross Motor Function Classification-Metachromatic Leukodystrophy.
Note: Severe motor impairment-free survival is defined as the interval from birth to the earlier of loss of locomotion and sitting without support (GMFC-MLD level 5 or higher) or death from any cause; otherwise, subject is censored at the last GMFC-MLD assessment date.

[1] van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: disease spectrum and approaches for treatment. Best Pract Res Clin Endocrinol Metab 2015; 29: 261–73.

Orchard therapeutics

OTL-200 (MLD): BLA Submission Completed; Moving Toward Potential Approval in 1H'24

BLA Submission and Approval Timeline

Oct. 2022
Externally-led patient focused drug development meeting with the FDA held by MLD patients and families with significant engagement from members of the BLA review team

Jan. 2023
Productive Type B meeting with the FDA to align on clinical package, including natural history, *etc*.

Apr. 2023
Pre-BLA meeting held with multi-disciplinary review team at the FDA to align on final BLA package, rolling BLA timeline and content of modules

Summary of Recent Regulatory Correspondence with the FDA

Nov. 2022
MLD Scientific Workshop held with the FDA by KOLs and treating physicians of the MLD community

Feb. 2023
Informal feedback meeting with the FDA after comprehensive CMC comparability reports submitted in 4Q '22

May 2023
Rolling BLA submission initiated

Rolling BLA Submission Completed

- ***BLA acceptance anticipated in Q3' 23***
- ***Potential approval in 1H' 24 assuming priority review***

Orchard therapeutics

Building Global Momentum for Libmeldy Commercial Potential

Commercial Activities

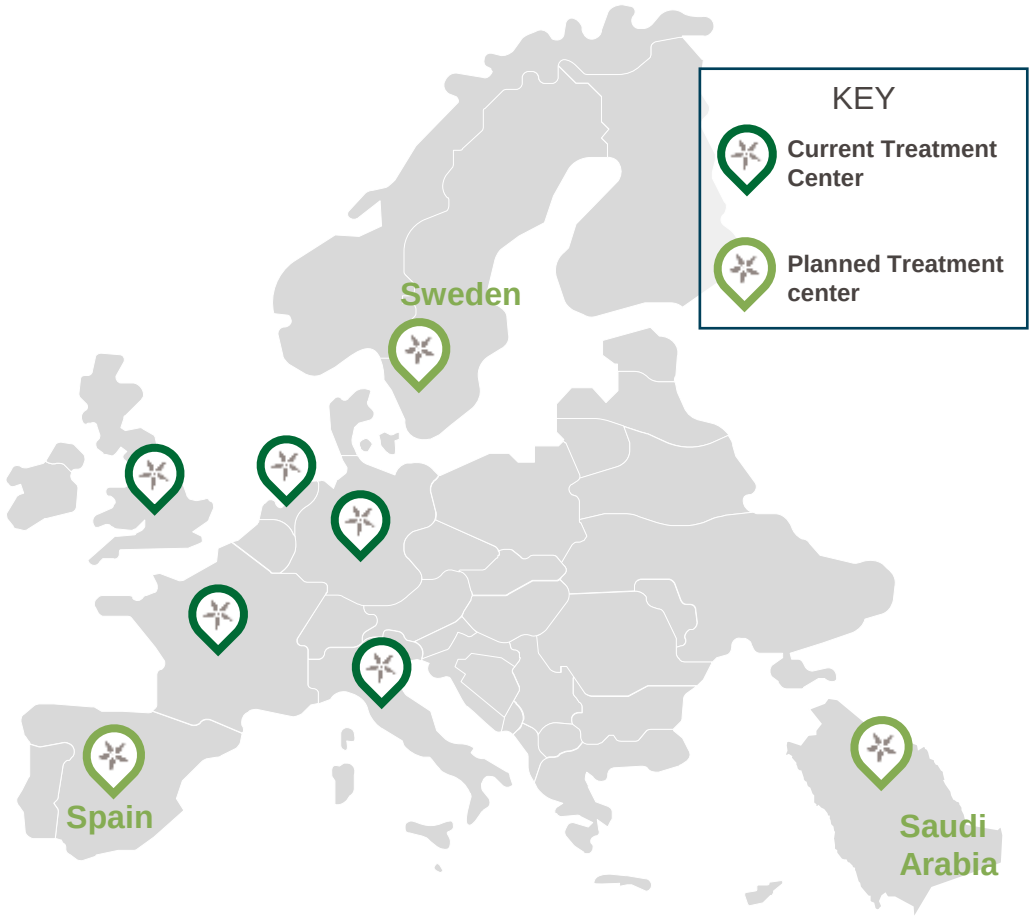
1) Newborn screening and disease awareness to drive patient ID
2) Broad access through qualified treatment center (QTC) network
3) Reimbursement through various pathways

Staged Areas of Focus

Orchard therapeutics

Expanding Reimbursed Access Throughout Europe

Access



Reimbursement

Secured for all eligible MLD children

Reimbursed early access (*e.g.*, France)

Cross border (S2) pathway: (*e.g.*, Central & Eastern Europe)

Treatment abroad: (*e.g.*, Middle East)

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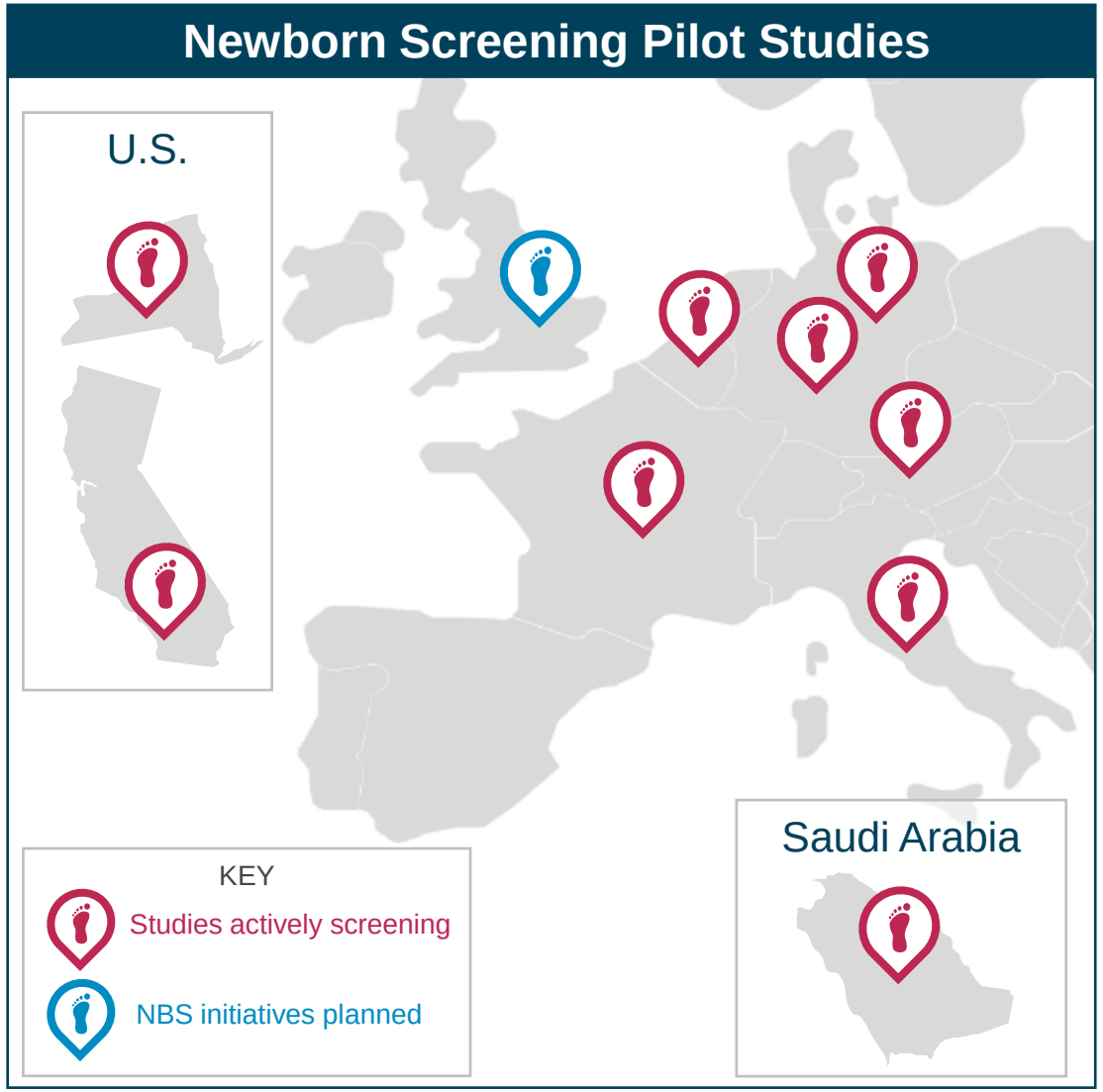
Implementing Newborn Screening to Identify MLD Patients



4 Confirmed cases of MLD following screening of **~150k** newborns

- ✓ Advancing universal newborn screening for MLD
  - Newborn Metabolic Screening Act (SB67) enacted in Illinois, MLD being added to statewide panel
  - Following study data, application for nationwide screening progressing in Germany
- ✓ Continuing to expand NBS initiatives in Europe, the U.S. and the Middle East

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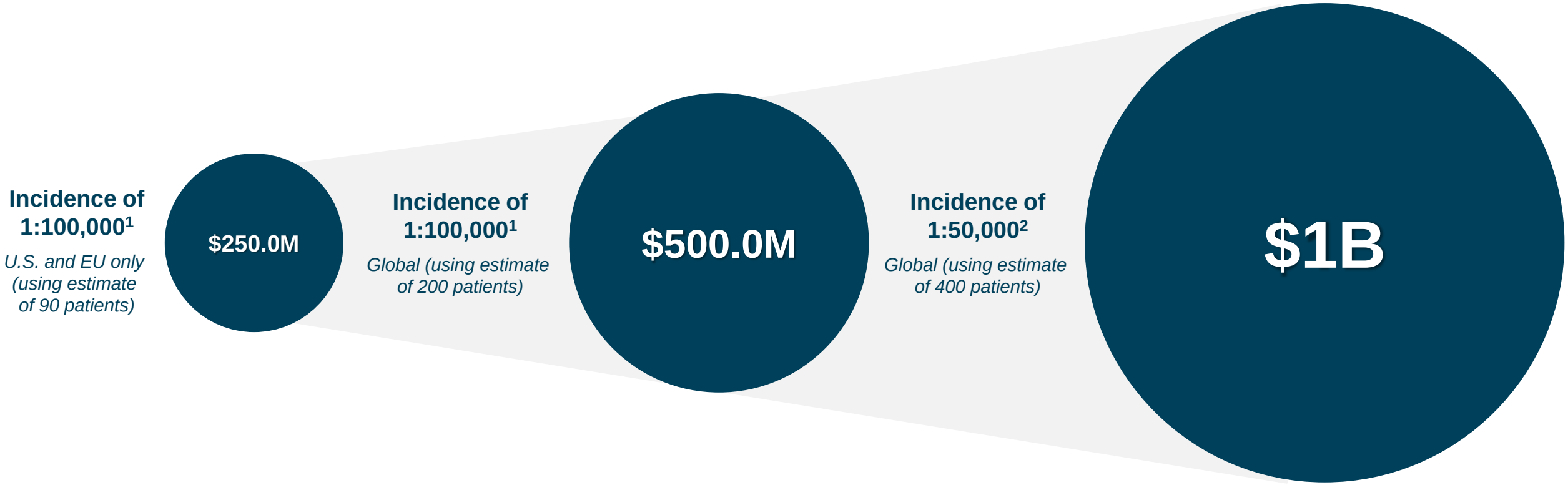
MLD Represents a Significant Annual Global Market Opportunity



Potential annual market opportunity for Libmeldy across all patient segments assuming an average per patient net price of $2.5M and universal newborn screening[3]

1. *von Figura K, Jaeken J. Metachromatic leukodystrophy. In: Scriver CR, Valle D, WS S, eds. The metabolic and molecular bases of inherited diseases. Mac Graw-Hill; 2001:3695-3724, chap. 148.*
2. *Based on four MLD cases identified following ~150,000 newborns screened through ongoing research studies as of June 30, 2023.*
3. *The sale price of Libmeldy will vary from jurisdiction to jurisdiction and could vary for a variety of reasons, some of which are outside of the company's control. The net price utilized on this slide is for illustrative purposes only and is not an estimate or prediction of the average net price of Libmeldy globally.*

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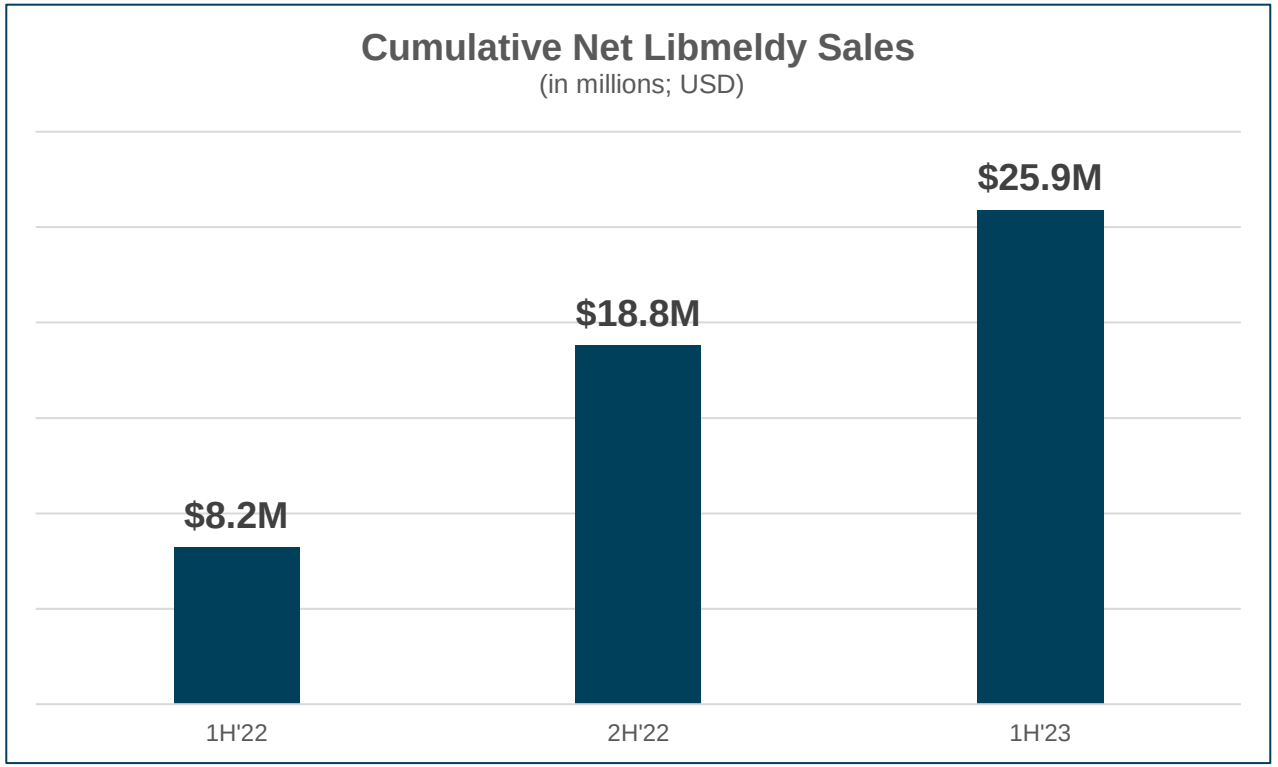
Steady Libmeldy Revenue Growth Since Launch

- Patients from 6 different countries treated commercially at 4 of 5 qualified centers
- Reimbursement via access agreements, cross-border and named patient pathways
- Average vein-to-vein time of 55 days with 100% success in production
- Company on track for year-over-year revenue growth



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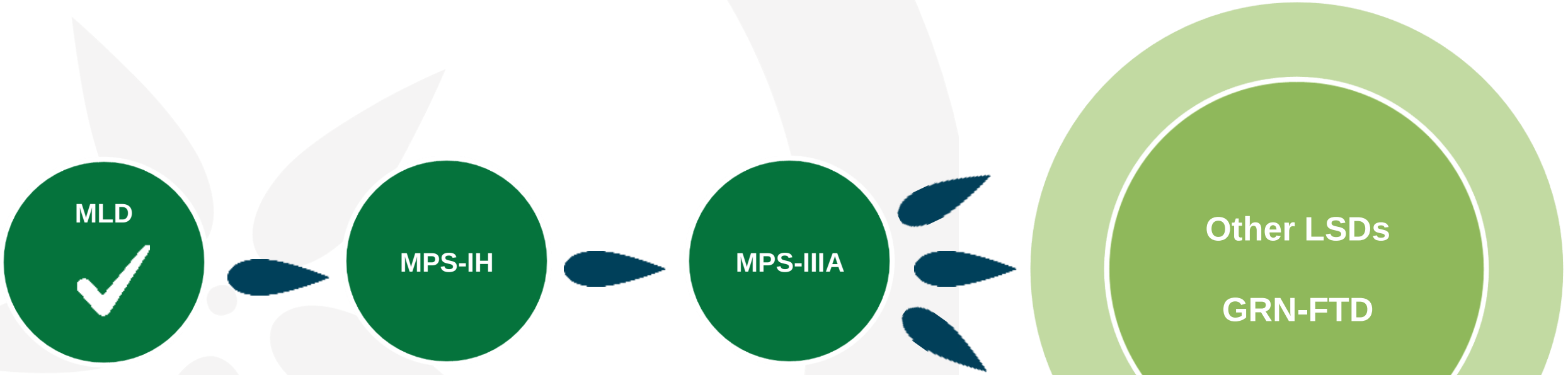
Success in MLD Provides Roadmap, Common Infrastructure for Next-in-line Neurometabolic and CNS Programs



Approved in Europe;
BLA submitted to U.S. FDA

PLATFORM SYNERGIES

Regulatory	Supply Chain
Manufacturing	Treatment Sites
Distribution	Referral Networks

Orchard therapeutics

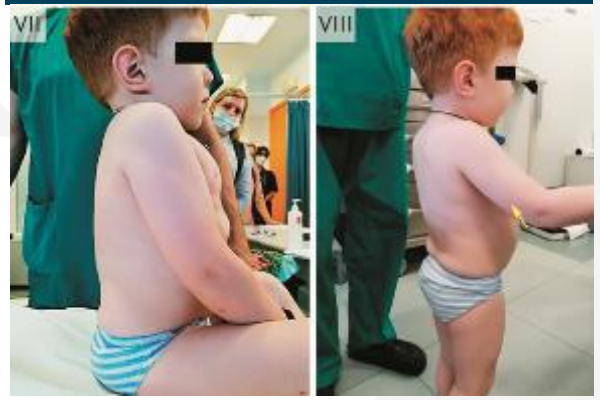
OTL-203 (MPS-IH): Disease Background & NEJM Interim PoC Results

MPS-IH

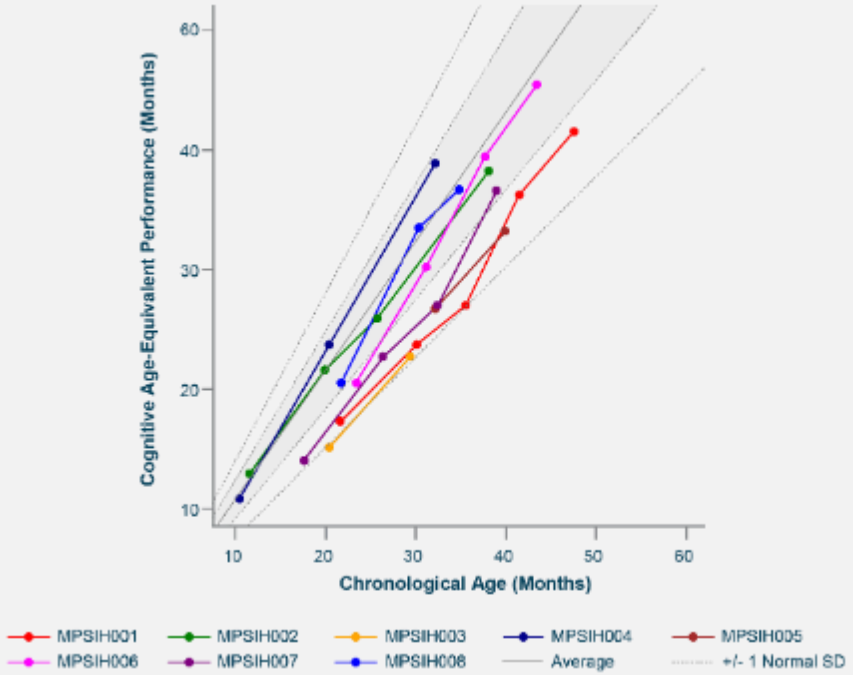
- Multisystemic neurometabolic condition affecting cognition, growth and skeletal function
- Current standard of care: HSCT and/or ERT as a bridging or chronic therapy
- ~1:100,000 live births; NBS established in some geographies, incl. U.S.

Before Gene Therapy

1.5Y after Gene Therapy



Neuropsychological Tests over Time
Cognitive Age-Equivalent Score (Overall)



Interim Proof-of-Concept (PoC) Study Results Published in NEJM

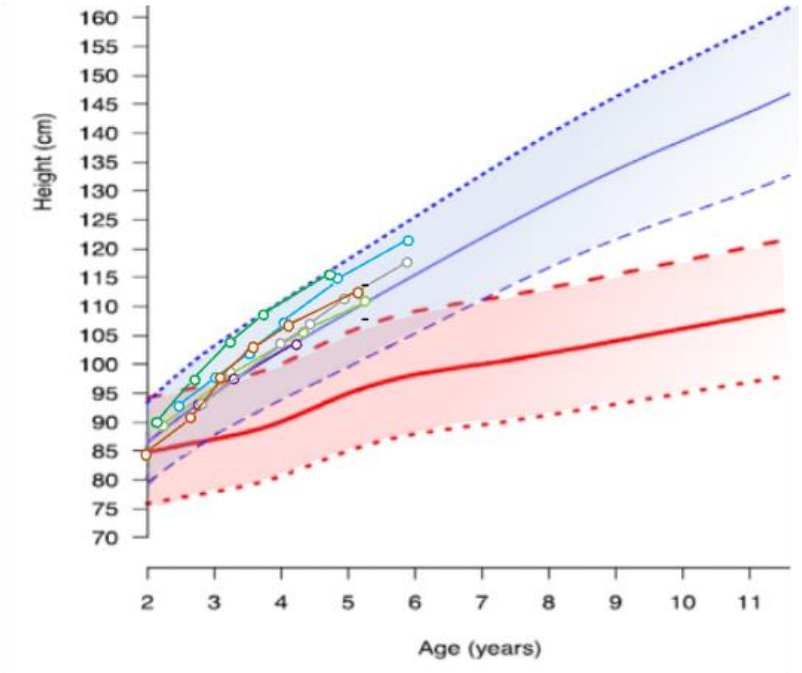
SD = Standard Deviation; IQ(C) = Intelligence Quotient (Cognition);
Engl J Med 2021; 385:1929-1940 DOI: 10.1056/NEJMoa2106596

Orchard therapeutics

OTL-203 (MPS-IH): Early Clinical Skeletal Outcomes Presented at ASGCT

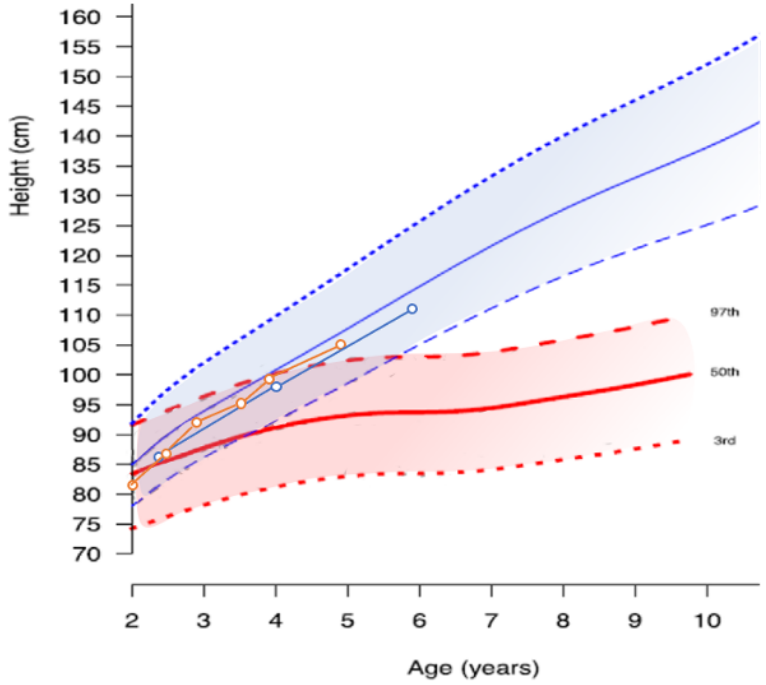
All GT pts. exhibit longitudinal growth within expected reference ranges according to age and gender, with a median height gain greater than the one observed in an external cohort of HSCT patients following a 3-year follow-up. [Short stature defined as height -2 SDS]

Growth charts males



○ MPSIH001 ○ MPSIH002 ○ MPSIH004
○ MPSIH005 ○ MPSIH006 ○ MPSIH007

Growth charts females



○ MPSIH003
○ MPSIH008

Percentiles:
WHO growth charts in blue-shadowed
MPSIH growth charts in red-shadowed

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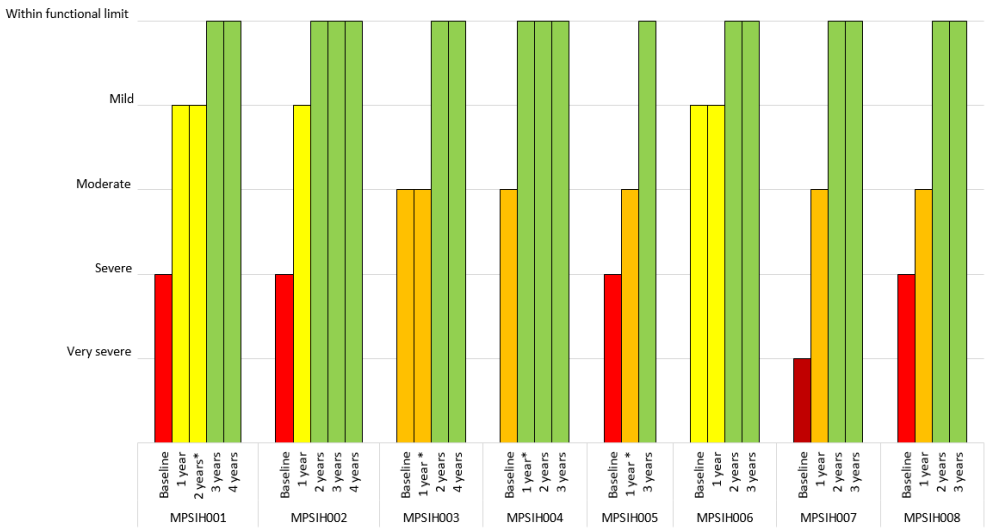
OTL-203 (MPS-IH): Patient Videos from ASGCT

Complete and earlier normalization of joint mobility (shoulder abduction and flexion, hip and knee extension ROM) as compared with an external cohort of HSCT pts.

TMQ by Peabody scale



MPSIH004,
36 months post GT

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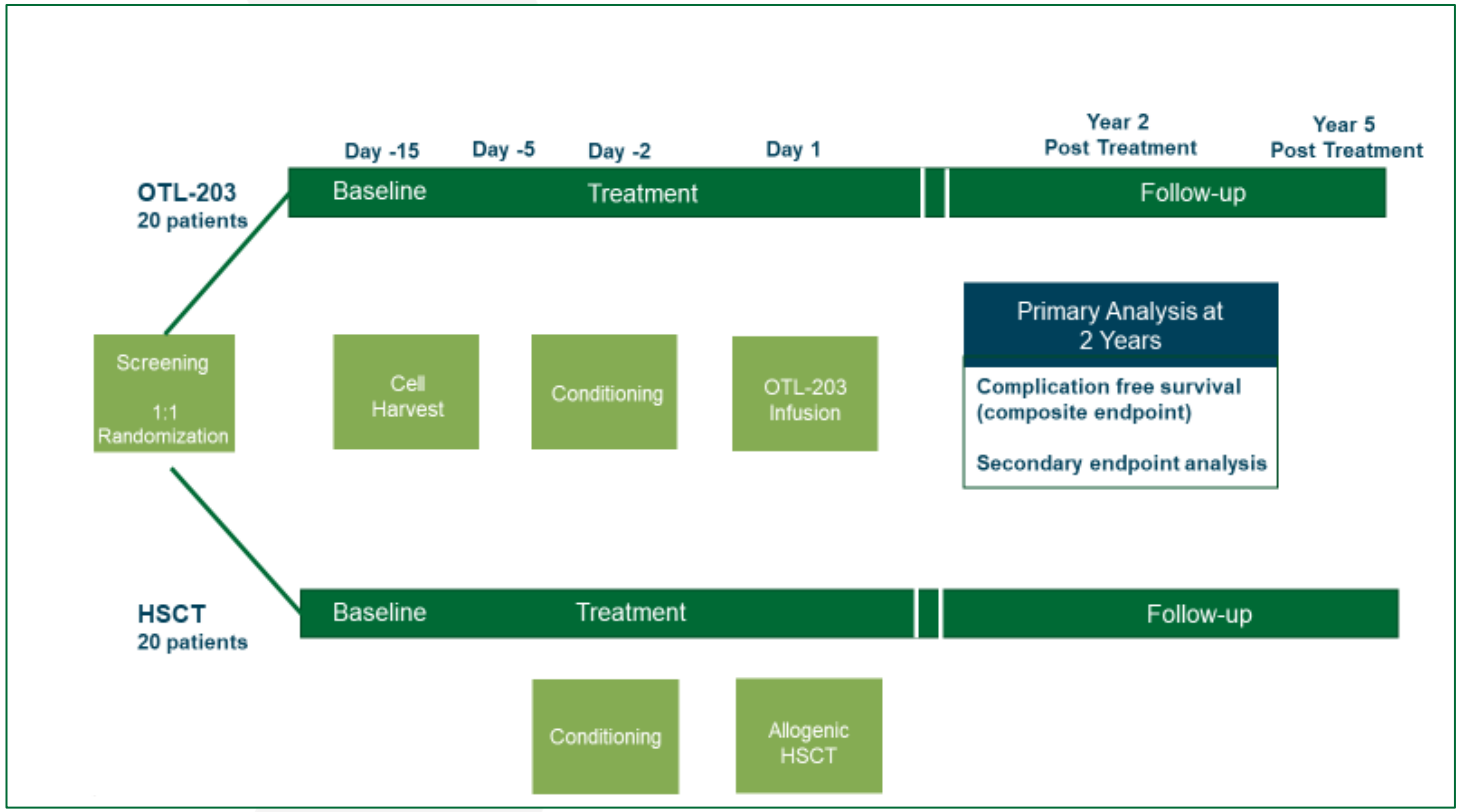
OTL-203 (MPS-IH): Moving into a Pivotal Trial in 2H 2023

- Randomized controlled trial vs. HSCT (standard of care)
- 40 patients
- 2-year primary analysis
- Composite endpoint
- Up to 6 U.S. / EU sites



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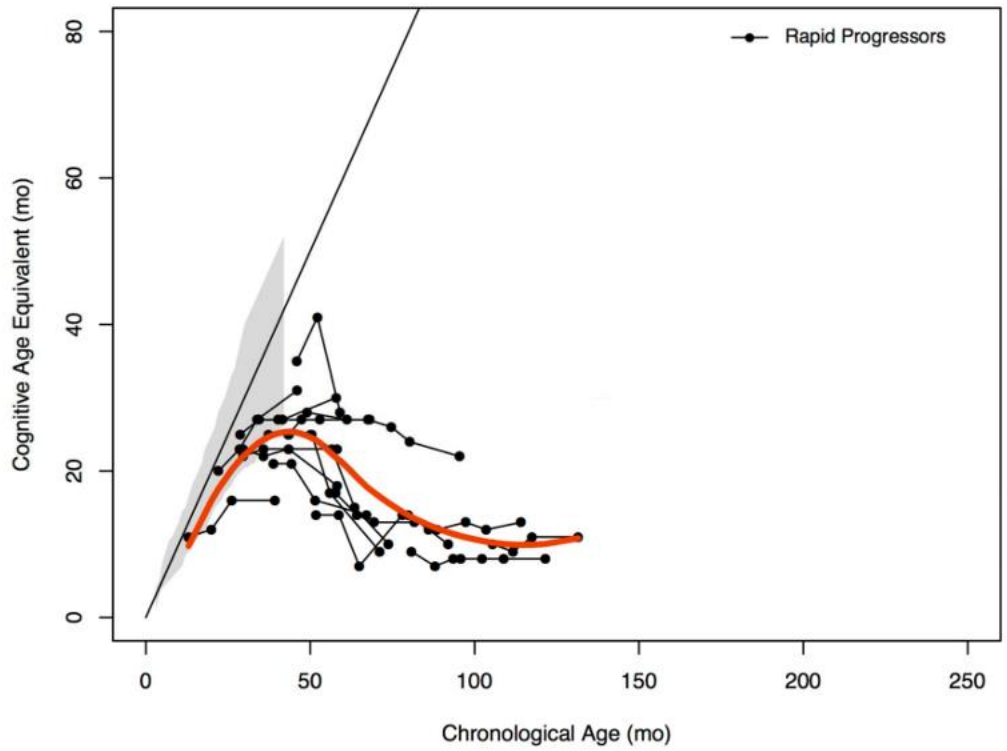
MPS-IIIA is a Progressive and Devastating Disease

- **Sanfilippo Syndrome type A;** pathogenic variants in ***SGSH* gene**
- Accumulation of **substrate heparan sulfate leading to severe CNS degeneration** w/ somatic manifestations
- **Severe phenotype** – development slows from 3 years of age, followed by cognitive decline, behavioural disturbances, loss of skills and eventual death
- **No successful treatment options**
  - Allogeneic HSCT shows *no modification* of disease phenotype despite wild type donor, full engraftment and early treatment
  - Robust correction of neurocognitive decline and durability of effect *not established* for AAV approaches
- **Incidence: ~1 in 100,000 live births**

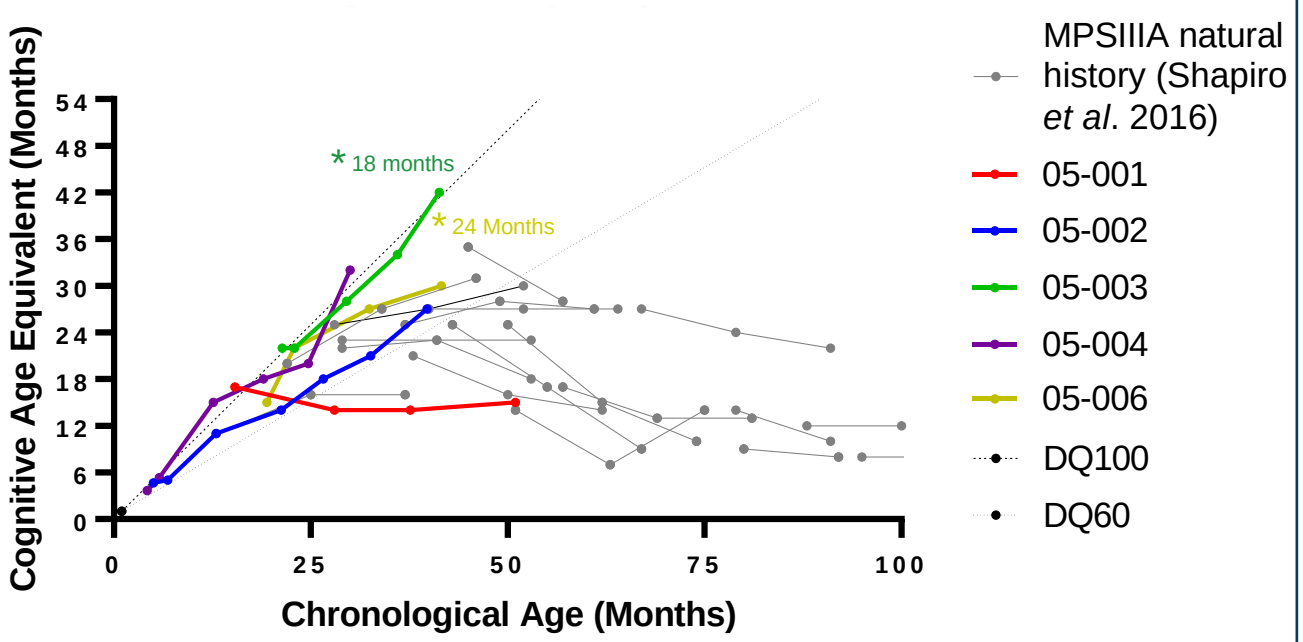


SGSH = N-Sulfoglucosamine Sulfohydrolase
Shapiro EG, et al. J Pediatr 2016;170:278-87.
Photos adapted from Natural History of Sanfilippo Syndrome in Spain; Orphanet Journal of Rare Diseases · December 2013

Neurocognitive Outcomes

- Patient 05-003 and 05-006 reached the ceiling of the Bayley scale (BSID-III) at 18/24 months and progressed onto the Kaufmann assessment (KABC-II) at 24/30 months
- Patient 05-003 is the first MPSIIIA patient with rapidly progressive phenotype at Manchester able to complete the Kaufman assessment
- Patient 05-003 is within normal range on Kaufmann scale at both 24- and 30-months post-transplant with gain in skills between assessments

Developmental Age Equivalent



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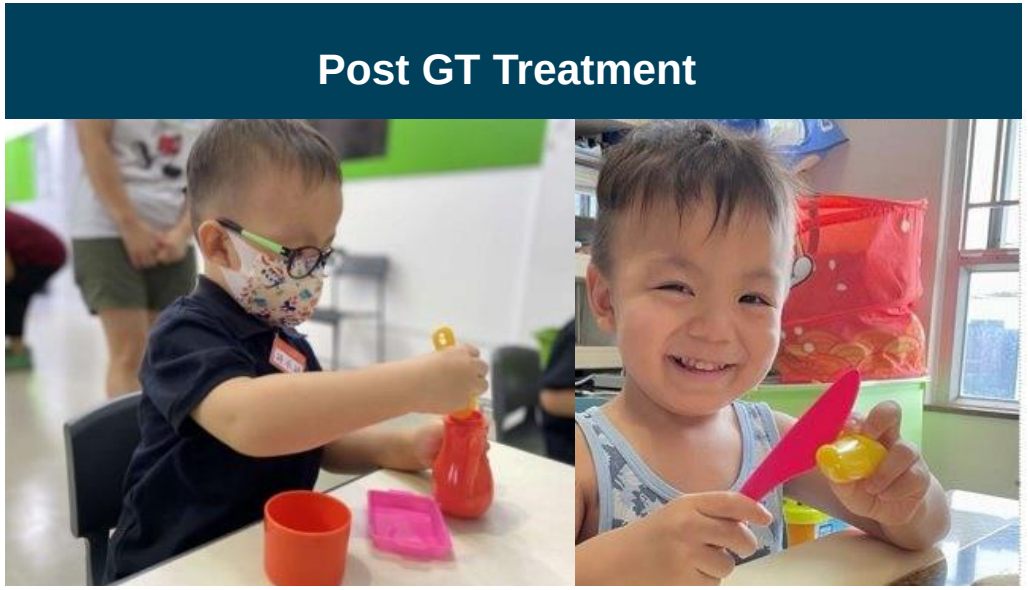
Neurocognitive Outcomes

Change **in cognitive function (age equivalent scores)** against natural history of MPSIIIA

Change in patient behavior, patient QoL and daily living

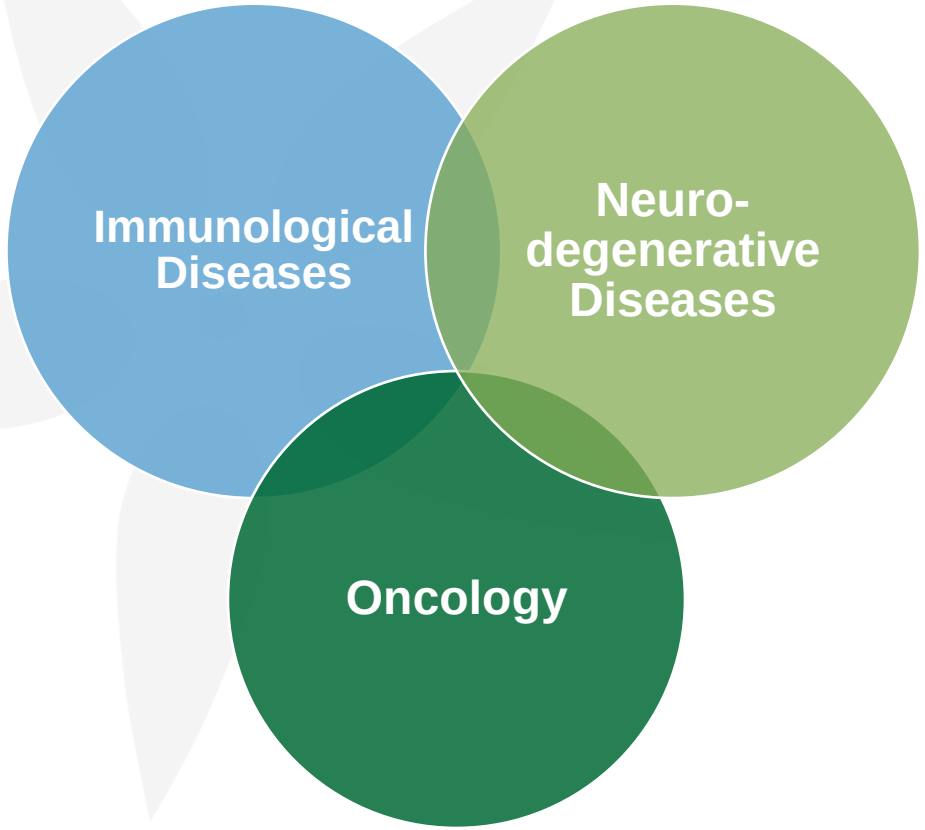
Early follow-up in trial patients

- **Gain of skills in line with development of normal children in 4 out of 5 patients**
- Developmental gains not seen in untreated MPSIIIA, e.g. acquisition of speech, continence and complex play
- Longer follow up needed to assess safety and efficacy outcomes



Orchard therapeutics

Our Platform Provides Multiple Opportunities for Business Development



Partnerships in specific diseases

- **OTL-105** for HAE partnered with Pharming
- Ongoing programs in CNS **(FTD)** and colitis **(NOD2-Crohn's)**

Partnerships built on specific technologies

- **Antigen-specific Tregs** for autoimmune diseases
- **mAb vectorization technology** to target specific tumors or other targets

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Executing on Key Corporate Milestones

Approximately $155.0M in Cash and Investments as of Q2'23 Supports Runway to mid-2025

Libmeldy - Commercial

- ✓ Secured reimbursed access in four additional European markets
- Add to qualified treatment center network
- Expand newborn screening activities to screen 200,000 babies by year-end
- Grow Libmeldy revenue year-over-year

Regulatory

- ✓ **OTL-200:** Completed rolling BLA submission to U.S. FDA in MLD
- **OTL-200:** BLA acceptance expected in Q3 w/ potential approval in 1H'24 assuming priority review

Development

- ✓ **OTL-201:** Report biochemical / clinical data from ongoing MPS-IIIA PoC study in 2023
- **OTL-203:** Initiate global registrational trial for MPS-IH in 2H 2023

Preclinical

- ✓ **OTL-204:** Report preliminary preclinical PoC data for GRN-FTD
- ✓ **OTL-104**: Report preclinical PoC data for NOD2-CD (1H 2023)
- **OTL-104:** Initiate IND-enabling activities ahead of 2025 planned IND submission

Advance other preclinical pipeline programs (*e.g.*, OTL-105) and enabling technologies (*e.g.*, HSC Tregs)

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Strategic Anchors Represent Breakout Opportunities for Orchard

All based on a HSC GT scientific and clinical platform

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