Orchard therapeutics™

Jefferies Virtual Global Healthcare Conference

June 3, 2020

Forward Looking Statements

Certain information set forth in this presentation and in statements made orally during this presentation contains “forward-looking statements”. Except for statements of historical fact, information contained herein constitutes forward-looking statements and includes, but is not limited to, the Company’s expectations regarding: (I) the safety and efficacy of its product candidates; (II) the expected development of the Company’s business and product candidates; (III) the timing of regulatory submissions for approval of its product candidates; (IV) the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates; (V) the timing of announcement of clinical data for its product candidates and the likelihood that such data will be positive and support further clinical development and regulatory approval of these product candidates; (VI) the likelihood of approval of such product candidates by the applicable regulatory authorities; (VII) the adequacy of the Company’s manufacturing capacity and plans for future investment; (VIII) execution of the Company’s vision and growth strategy, including with respect to global growth; (IX) the size and value of potential markets for the Company’s product candidates; and (X) projected financial performance and financial condition, including the sufficiency of the Company’s cash, cash equivalents and investments to fund operations in future periods and future liquidity, working capital and capital requirements. The words “may,” “should,” “expects,” “intends,” “plans,” “anticipates,” “believes,” “estimates,” “predicts," “potential,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements are provided to allow investors the opportunity to understand management’s beliefs and opinions in respect of the future so that they may use such beliefs and opinions as one factor in evaluating an investment.

These statements are neither promises nor guarantees of future performance. Such forward-looking statements necessarily involve known and unknown risks and uncertainties, which include, without limitation, the severity of the impact of the COVID-19 pandemic on the Company’s business, including on clinical development and commercial programs, which may cause actual performance and financial results in future periods to differ materially from any projections of future performance or results expressed or implied by such forward-looking statements. You are cautioned not to place undue reliance on forward-looking statements. These statements are subject to a variety of risks and uncertainties, many of which are beyond the Company’s control, which could cause actual results to differ materially from those contemplated in these forward-looking statements. For additional disclosure regarding these and other risks faced by the Company, see the disclosure contained in the Company’s public filings with the U.S. Securities and Exchange Commission (the “SEC”), including in the Company’s annual report on Form 10-K filed with the SEC on February 27, 2020, as well as subsequent filings and reports filed with the SEC. These forward-looking statements speak only as of the date of this presentation. The Company undertakes no 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.

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Global leader in hematopoietic stem cell gene therapy

Focused on rare inherited conditions with no or few treatments

Dedicated to transforming the lives of patients with rare diseases

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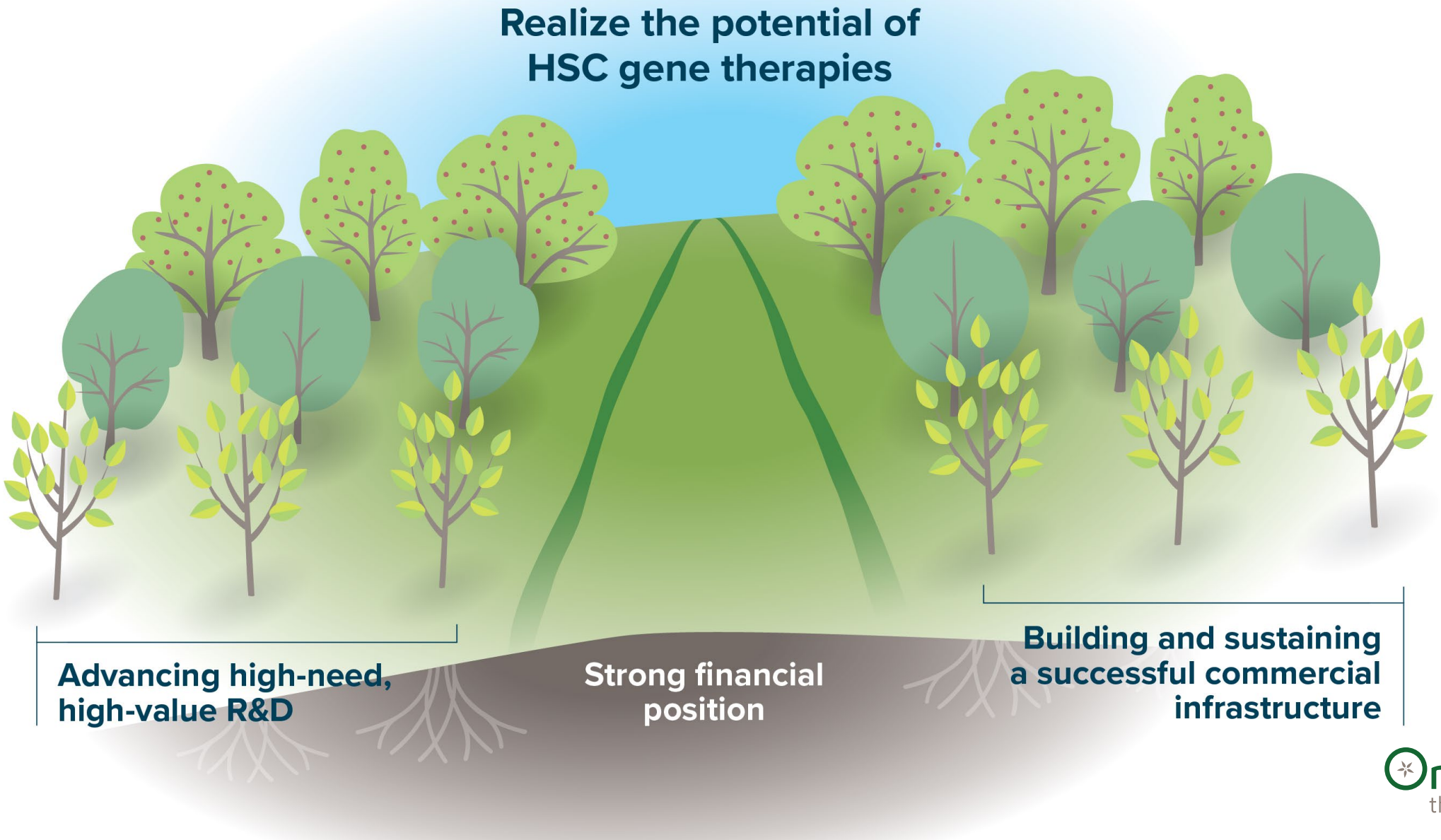
Orchard's Strategic Vision

Driven by Science and Backed by Strong Fundamentals



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Realizing the potential of the HSC gene therapy approach
Core Elements of the New Strategic Plan

Prioritize portfolio investments

- Establish MLD, WAS and MPS programs as top near-term priorities
- Accelerate research in less rare indications, including two new programs in genetic subsets of FTD and Crohn's disease

Invest in next-generation manufacturing

- Prioritize investments in technology and process innovations and phase investment in future manufacturing capacity

Establish focused commercial model

- Phase commercial build to align with expected launch trajectories for OTL-200 (incidence-based opportunity) and OTL-103 (prevalence-based opportunity)

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HSC Platform Approach

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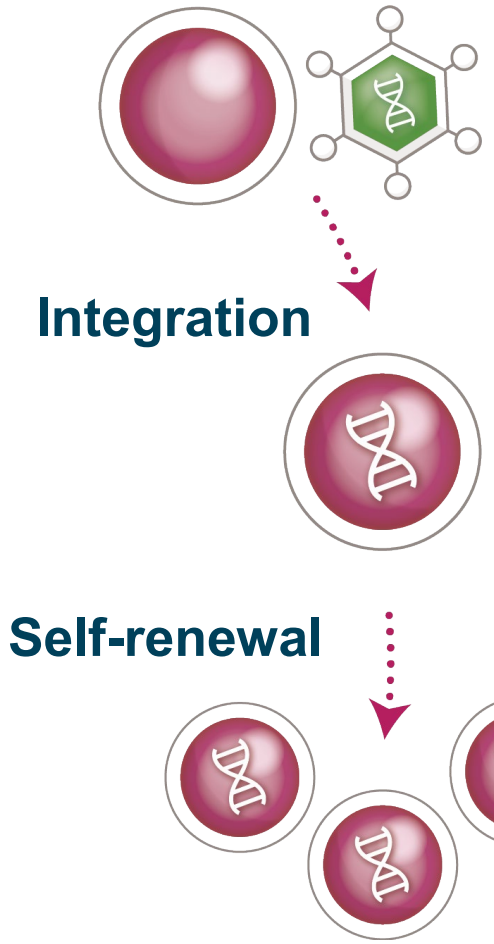
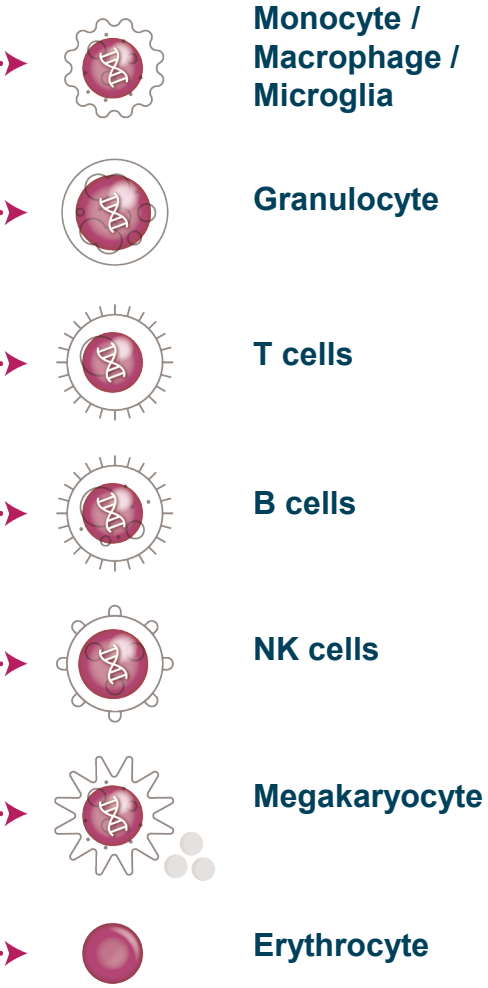
HSC Gene Therapy Offers a Highly Differentiated Approach



One-time administration

Potential for permanent disease correction

Differentiates into multiple cell types



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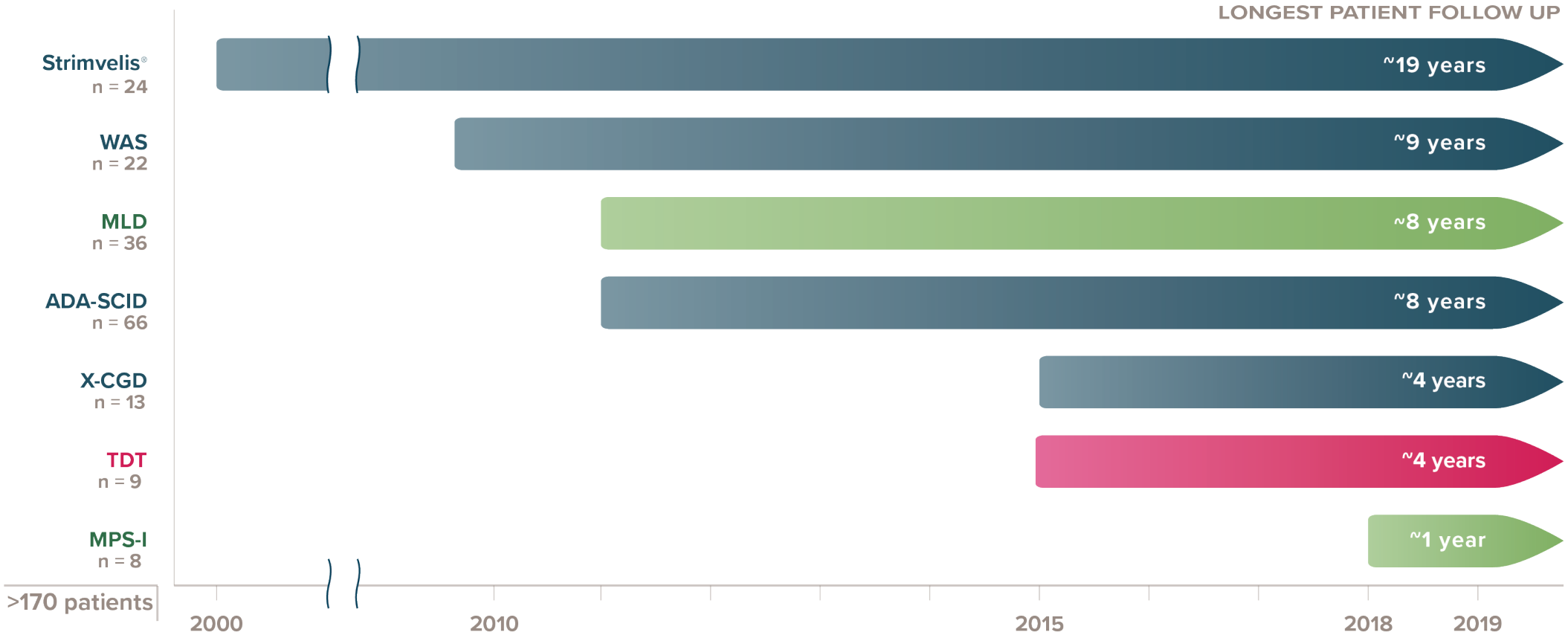
Durability of Response Demonstrated via Longest Patient Follow-up



Patients treated in the development phase, including in clinical trials and under pre-approval access (defined as any form of pre-approval treatment outside of a company-sponsored clinical trial, including, but not limited to, compassionate use, early access, hospital exemption or special license).
Patient with longest Strimvelis® follow-up enrolled in registry study, with data available up to 19 years.
Strimvelis was approved by the EMA in 2016. It has not been approved by the FDA.
Data based on in-house data as of December 2019.

Data include all patients treated with CD34+ hematopoietic stem cells transduced ex vivo with vector of interest.

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Our Work in Neurometabolic Disorders

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Metachromatic Leukodystrophy (MLD) is a Devastating, Rapidly Progressive Disease

Disease Snapshot

Age 5, pre-diagnosis

Age 9, advanced disease

- Fatal genetic CNS disorder
- Relentless loss of physical and cognitive function
- Presents on a spectrum with different ages of onset

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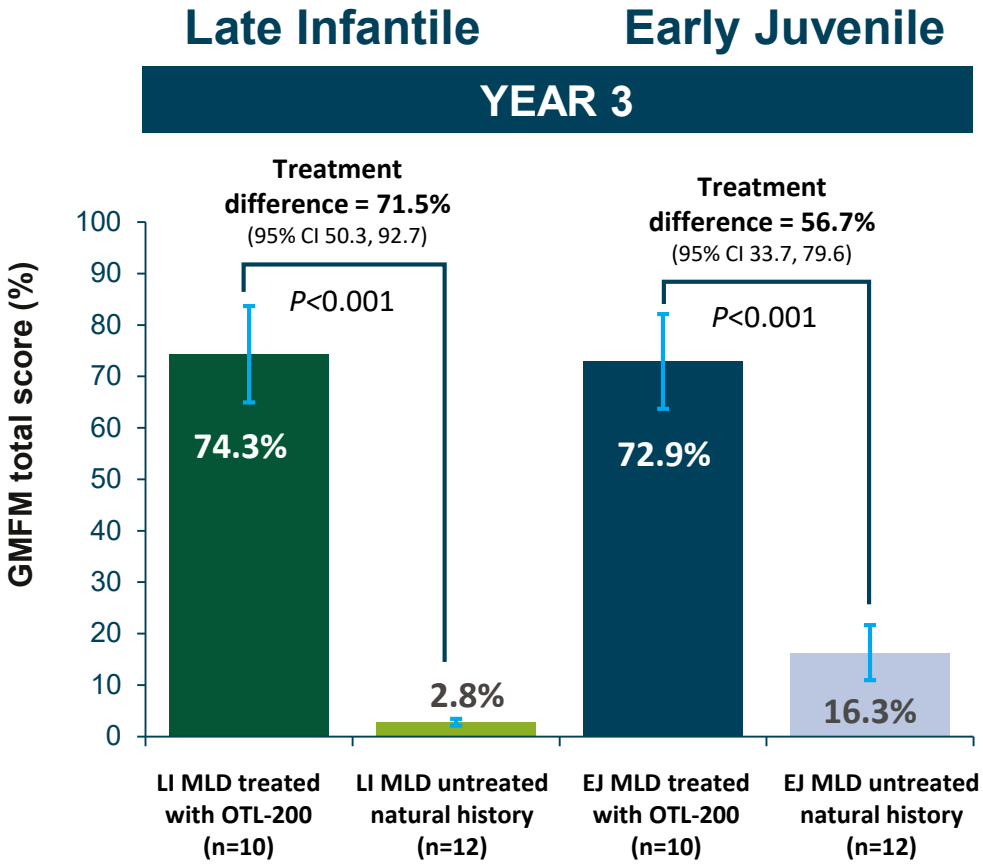
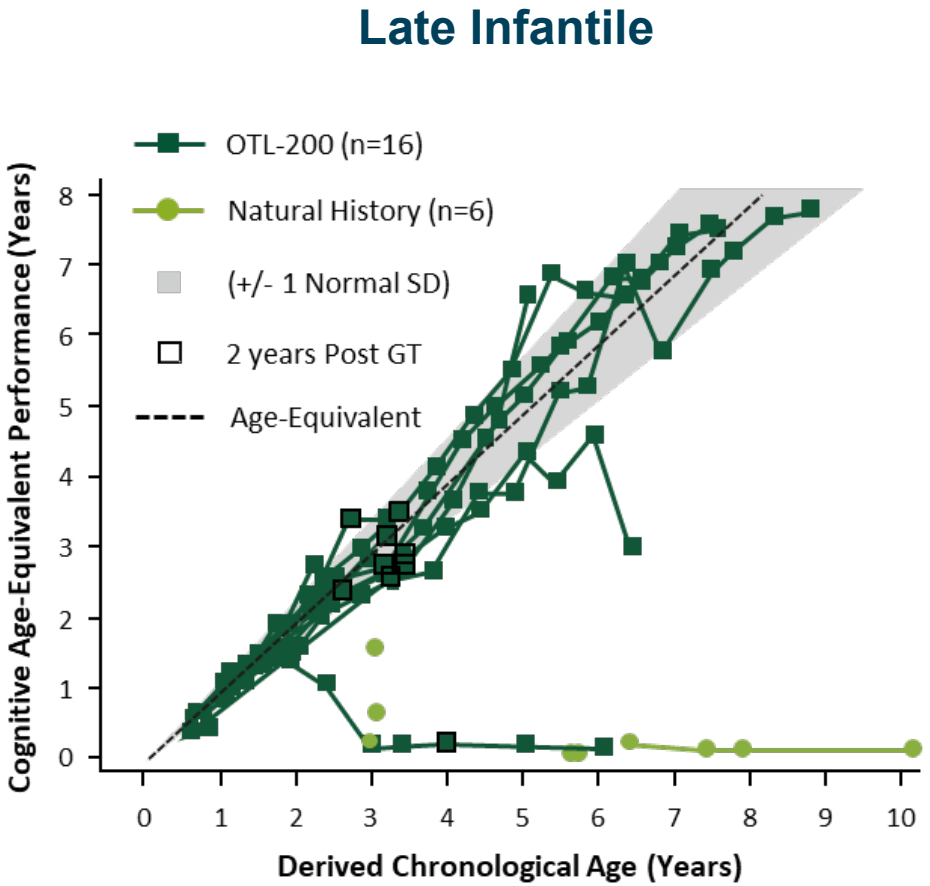
OTL-200 for MLD: Significantly Superior Motor and Cognitive Function Demonstrated vs. Natural History



Both LI and EJ patients achieved a statistically significant difference on the co-primary endpoint of improvement of >10% of the total GMFM score in treated subjects when compared to the Natural History cohort at Year 2, and these were maintained through Year 3. Note: vertical error bars are SE of the adjusted mean; P-values are from a two-sided 5% hypothesis test with null hypothesis of ≤ 10% difference ;CI, confidence interval; EJ, early juvenile; GMFM, gross motor function measurement; LI, late infantile; MLD, metachromatic leukodystrophy.



Cognitive Age-Equivalent at each visit has been derived as follows: For WPPSI and WISC: (DQp x Chronological Age)/100. For Bayley III: Cognitive Raw Scores have been compared to the tabulated values in the Bayley III manual to calculate Cognitive Age-Equivalent. For Bayley II: Cognitive Age-Equivalent is based on Mental Development Age as reported on the CRF. The Psychological Corporation. 2006.Bayley N. Bayley scales of infant and Toddler Development. Third Edition. San Antonio.

Integrated analysis presented September 4 2019 at SSIEM annual meeting

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MPS-I is a Highly Debilitating Condition Impacting Cognitive, Skeletal and Cardiorespiratory Function

Disease

- Deficiency of IDUA enzyme > accumulation of heparan and dermatan sulfate
- Severe cognitive defects as well as extensive somatic pathologies (skeletal dysplasia, cardiomyopathy, loss of vision and hearing)

Epidemiology

- Incidence estimated at ~1 in 100,000 live births
- Hurler syndrome (most severe phenotype) accounts for 60% of MPS-I

Current Treatment Options

- Hematopoietic stem cell transplantation (standard of care for <2.5 years)
  - Prolongs survival and partially stabilizes cognitive development if treated early
  - Residual disease burden (especially on the skeleton)
- Enzyme replacement therapy
  - Early use can improve some clinical features in non-Hurler patients
  - Limited efficacy on neurological and bone disease




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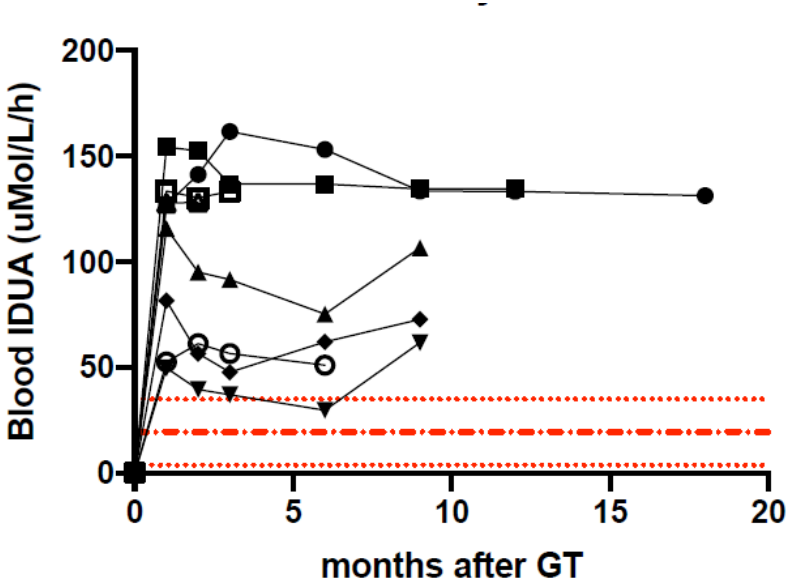
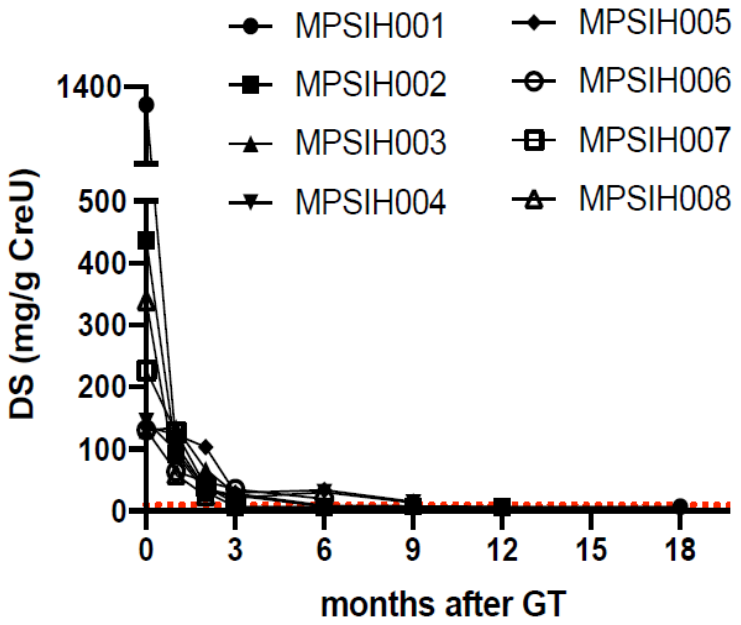
OTL-203 for MPS-I: Encouraging Preliminary Clinical Biomarker Data Across 8 Patient Cohort

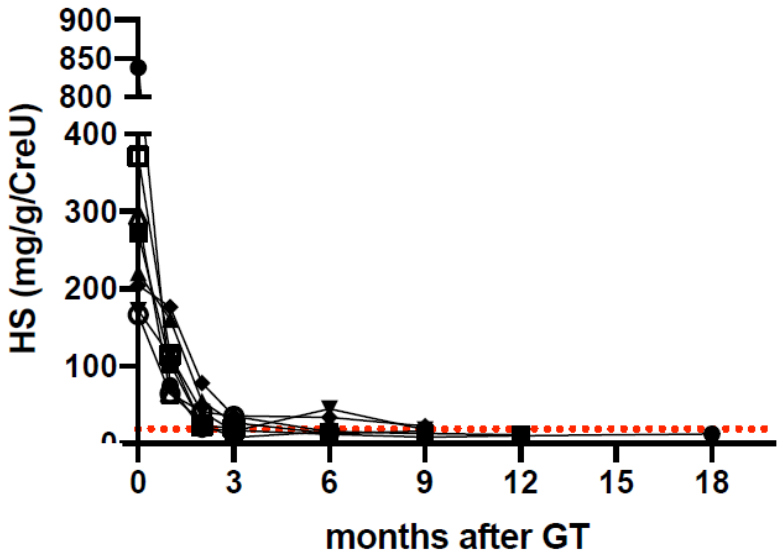
IDUA Activity on DBS



DS in Urine



HS in Urine



ULN
Normal (avg)
LLN

Normal values per age

DBS = dried blood spot
IDUA = Alpha-L-iduronidase
ULN = Upper limit of normal
LLN= Lower limit of normal
HS= Heparan sulfate
DS= Dermatan sulfate

Data presented May 15, 2020 at ASGCT annual meeting

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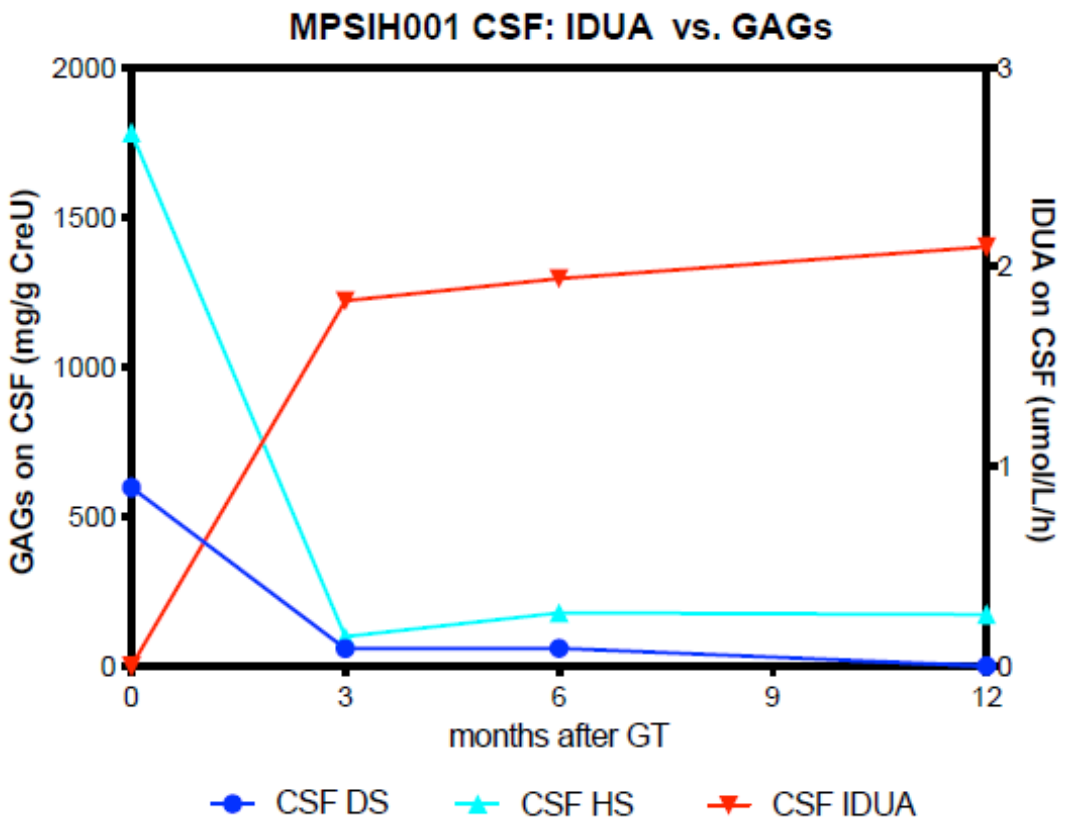
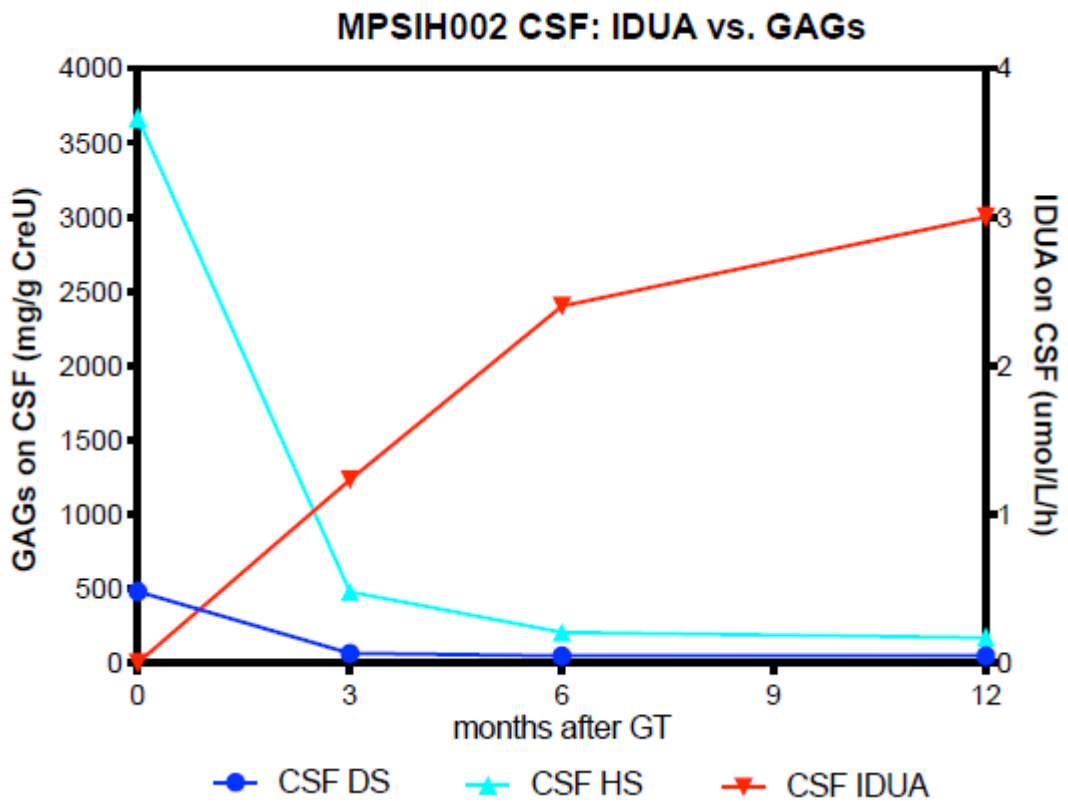
Reconstitution of IDUA Activity in CSF Paralleled by GAG Decrease in First Two Patients

IDUA Activity on CSF vs GAGs on CSF-MPSIH001



IDUA Activity on CSF vs GAGs on CSF-MPSIH002



Data presented May 15, 2020 at ASGCT annual meeting

IDUA = Alpha-L-iduronidase
CFS = cerebrospinal fluid
GAGs = glycosaminoglycans

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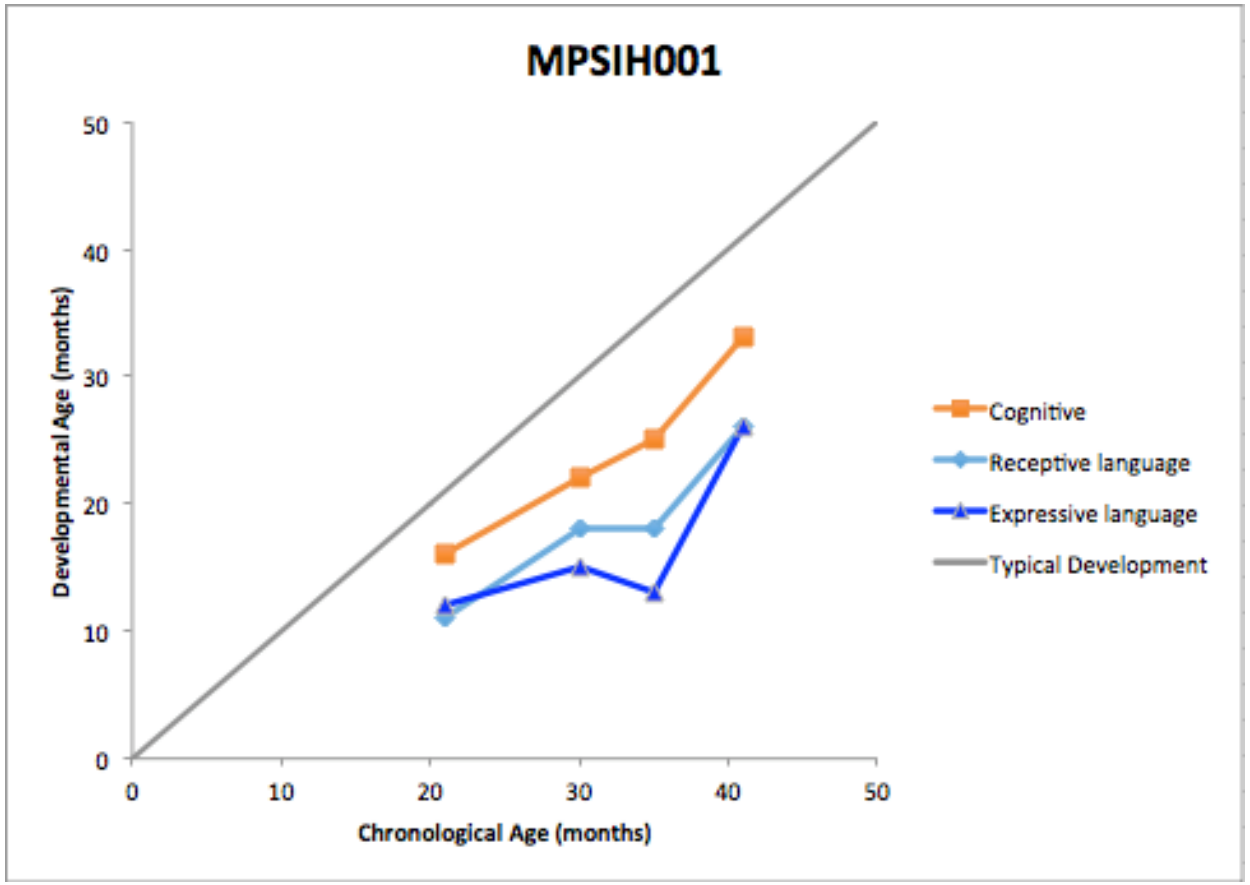
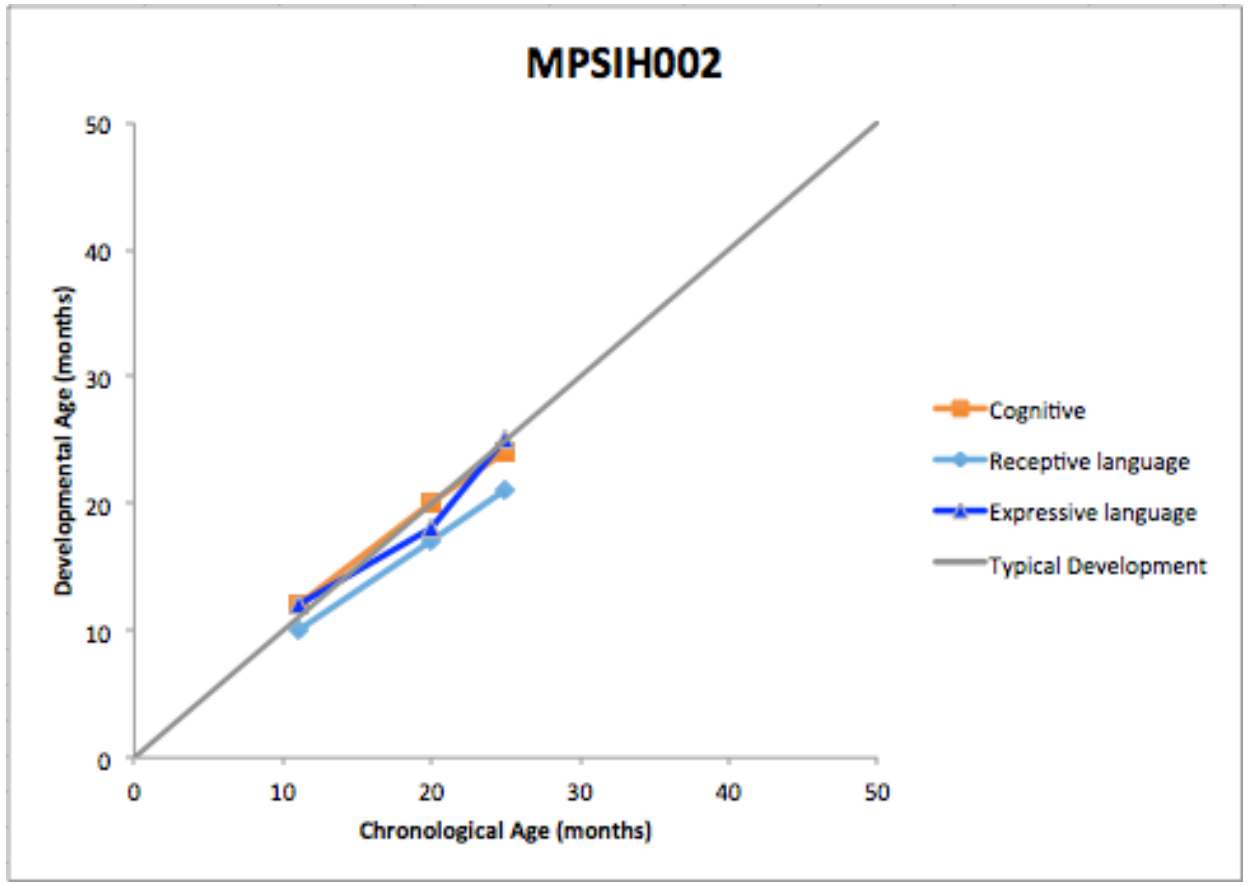
Preliminary Evidence of Clinical Efficacy

Stable Cognitive and Language Performances in First Two Patients Treated





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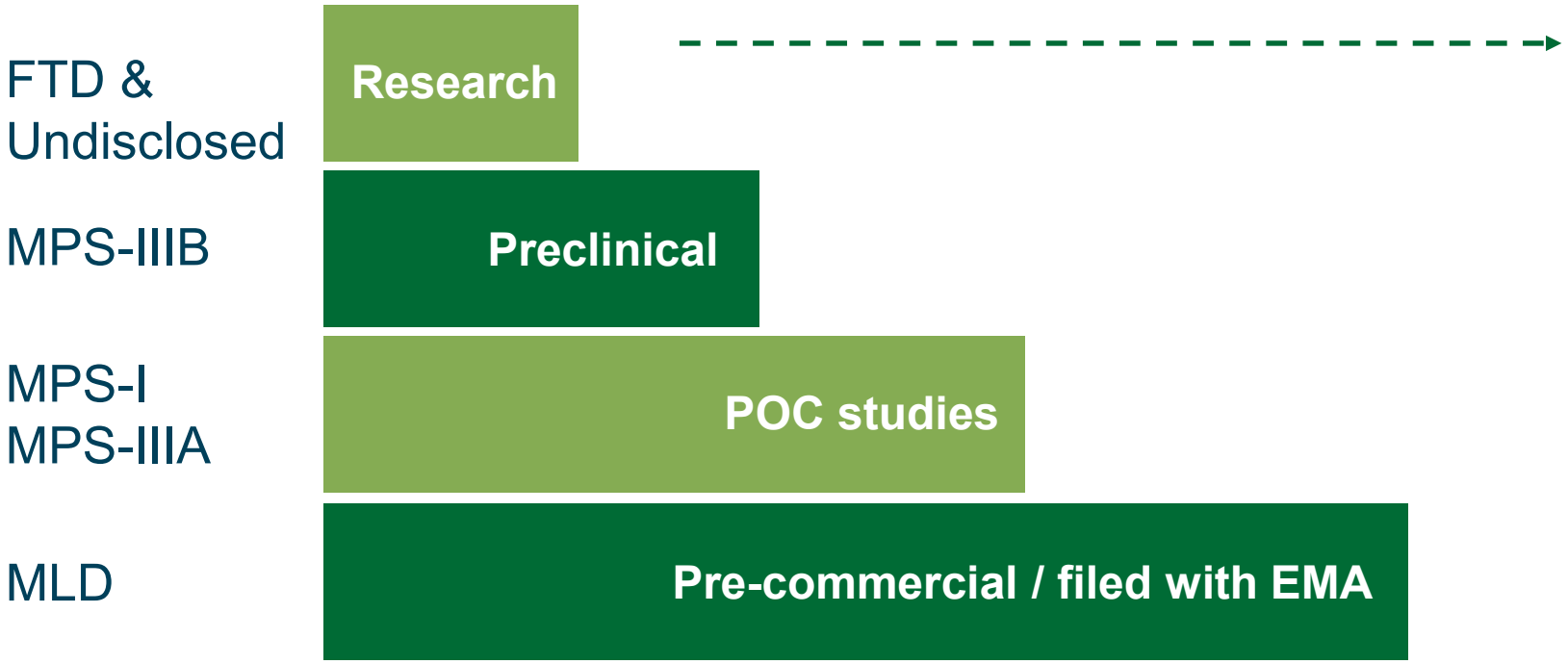
Building on our Strength in Neurometabolic Disorders



Brain

External collaboration with Dr. Alessandra Biffi

Boston Children's Hospital
Until every child is well™

Multiple new neurodegenerative disorders

Potential applications in larger / less-rare conditions

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Platform Extension into Less Rare Diseases

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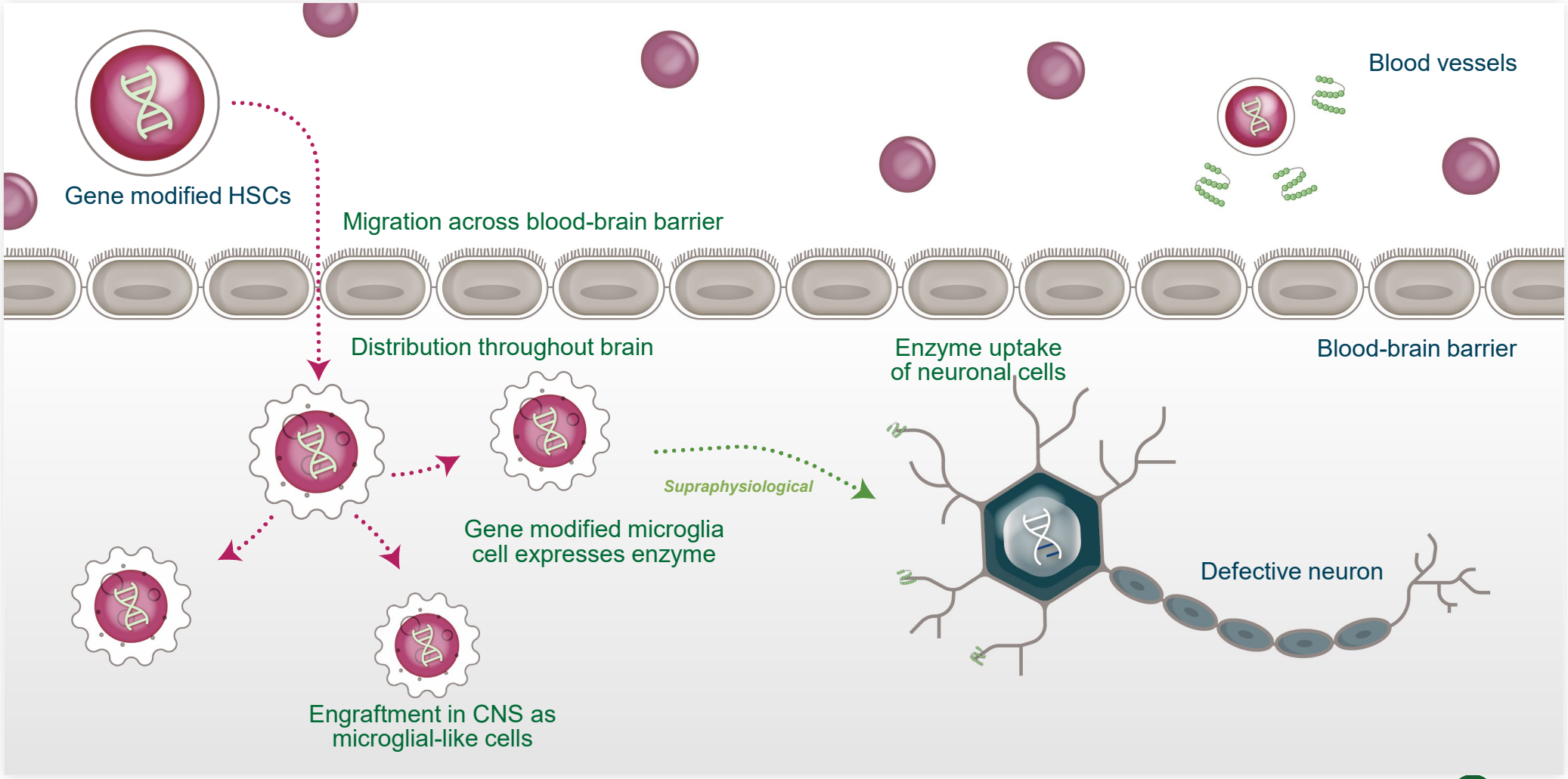
Delivering Proteins to Brain

Potential to Treat Multi-System Neurometabolic Diseases via Cross-Correction



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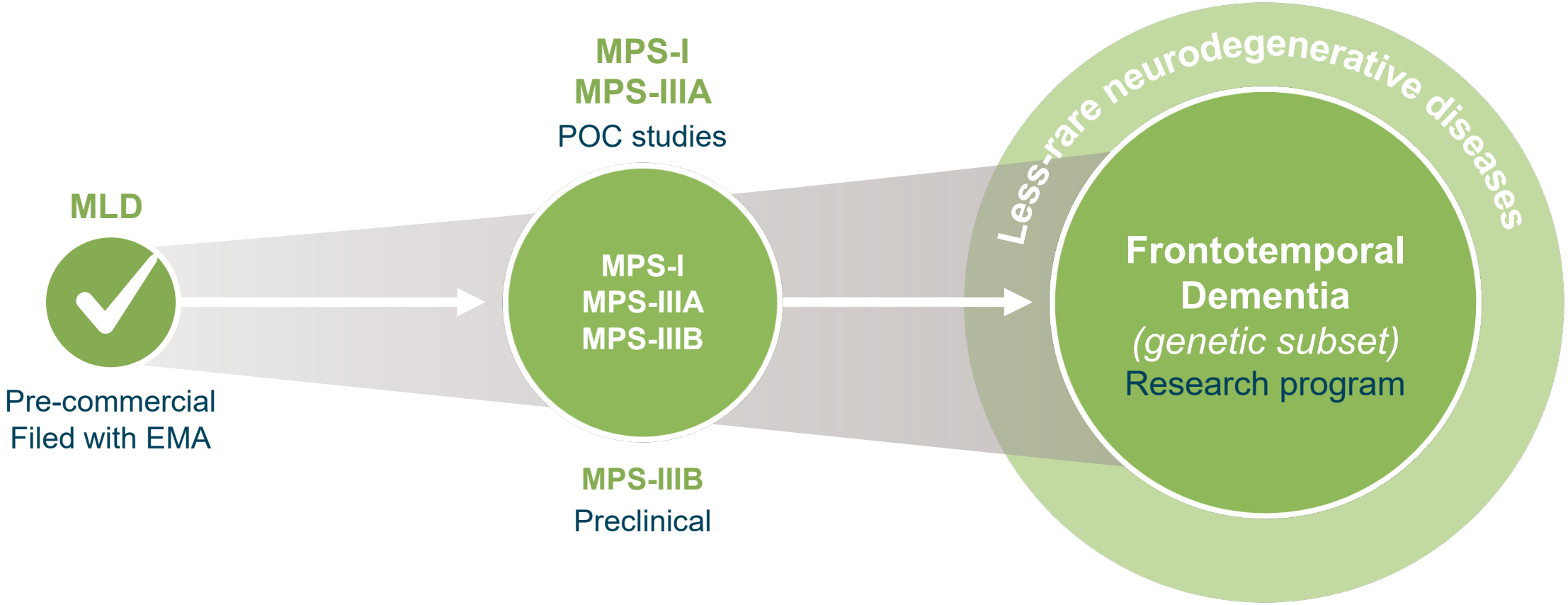
Clinical Validation in MLD Supports Application in Less Rare Populations such as Frontotemporal Dementia (FTD)



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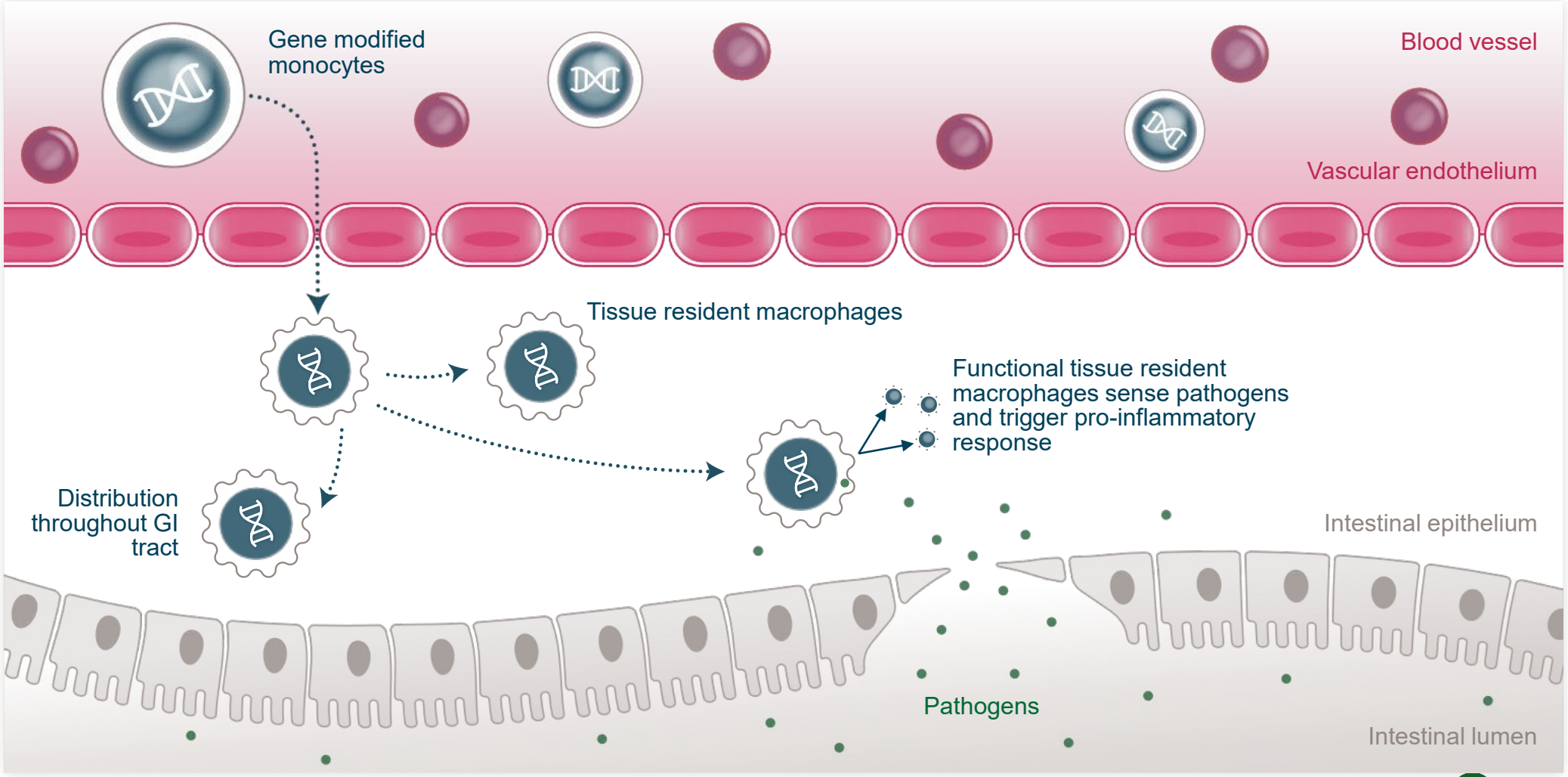
HSC-Derived Monocytes Can Repopulate Tissue Resident Macrophages



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Clinical Validation in X-CGD Supports Application in Less Rare Populations such as Crohn's Disease

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Commercial Readiness and Manufacturing

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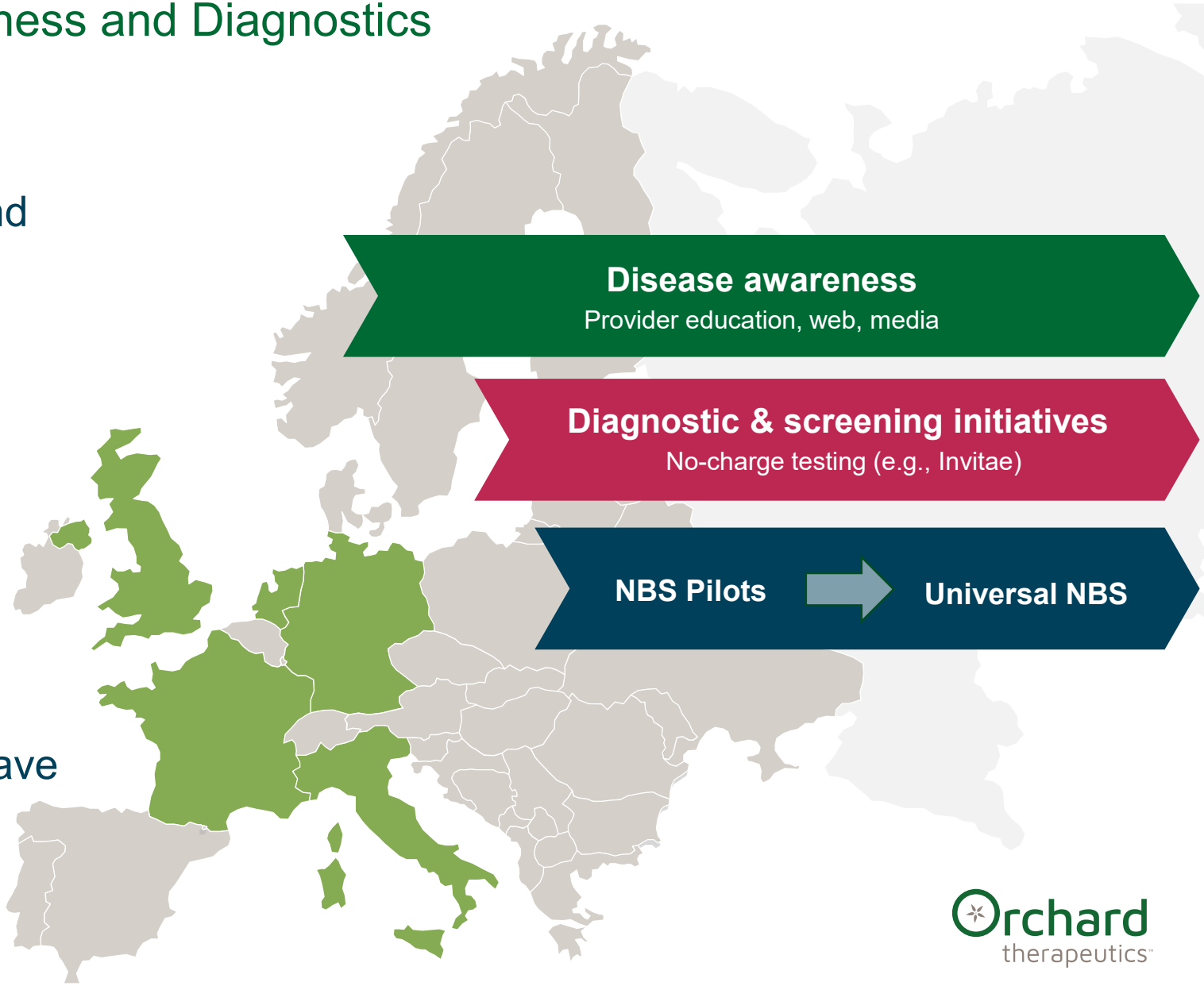
Preparing to Launch OTL-200 (MLD) in EU in 2021

Key Centers, Disease Awareness and Diagnostics

- Key centers of excellence for lysosomal storage disorders and transplant identified; site qualification ongoing
  - Germany
  - France
  - Italy
  - UK
  - The Netherlands
- Serve as foundation for next wave of neurometabolic programs (MPS-I, MPS-IIIA)



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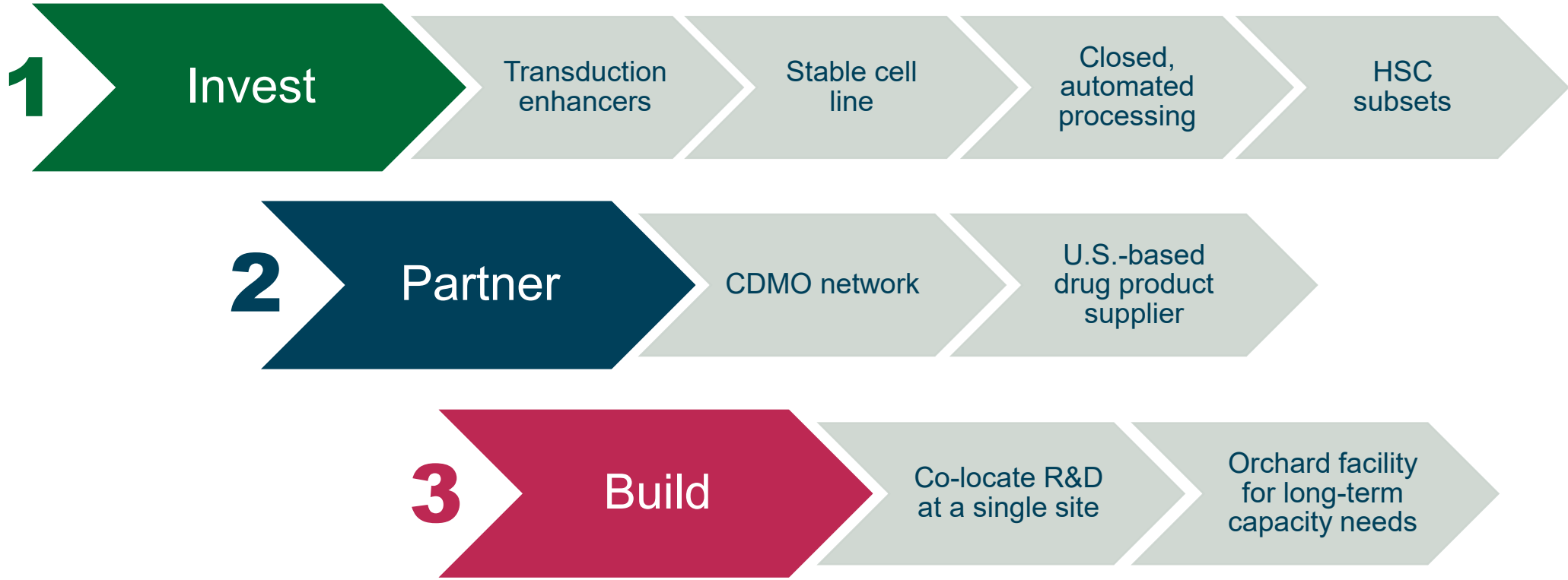
Three-Pronged Manufacturing Strategy Aligns Needs and Investments



Phased approach to investment in manufacturing designed to support needs of business and lower cost of capital

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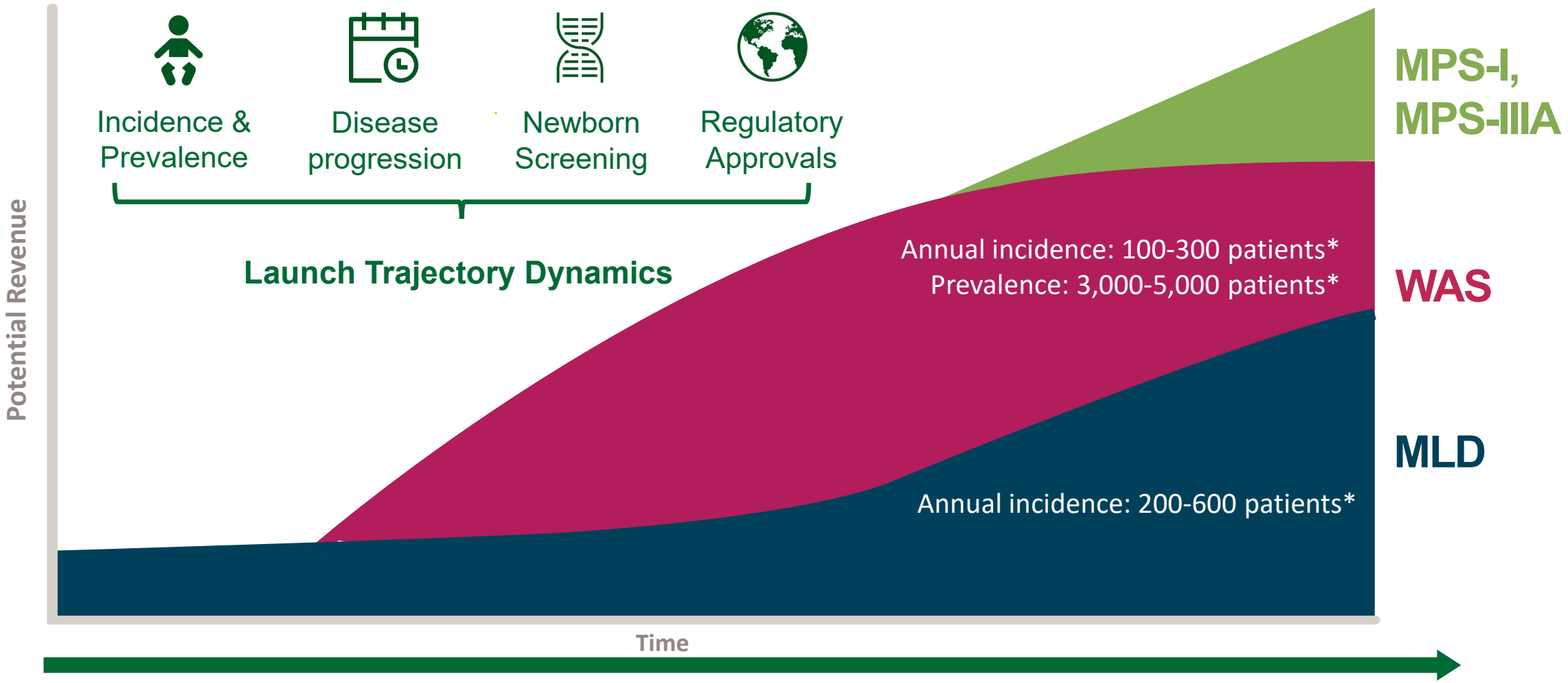
Significant Revenue Opportunity Across High-Value Programs



Commercial Build Ramps As Revenue Opportunity Grows Over Time - **Launch curves are illustrative and may vary**

* Incidence and prevalence figures are management estimates, based on available literature and population data in countries where rare disease therapies are typically reimbursed. Epidemiology sources include https://ghr.nlm.nih.gov/condition/metachromatic-leukodystrophy (MLD), https://ghr.nlm.nih.gov/condition/wiskott-aldrich-syndrome (WAS) and https://www.ncbi.nlm.nih.gov/pubmed/20399414 (WAS)

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Multiple Expected Milestones Over the Next 12-18 Months

MLD	Obtain approval for OTL-200 in EU in 2H 2020; launch in 1H 2021 Seek RMAT designation and file IND in U.S. in 2H 2020
WAS	Submit BLA and MAA filings for OTL-103 in 2021
MPS-I	Release OTL-203 interim POC data at ASGCT and in 2H 2020; Report one-year follow-up results and initiate registrational study in 2021
MPS-IIIA	Enroll 5 patients in OTL-201 POC study and release interim data in 2021
Research	Provide detail on pre-clinical development in FTD and Crohn's programs in 2020

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