Orchard therapeutics™

Corporate Presentation

November 2021

Forward-looking Statements

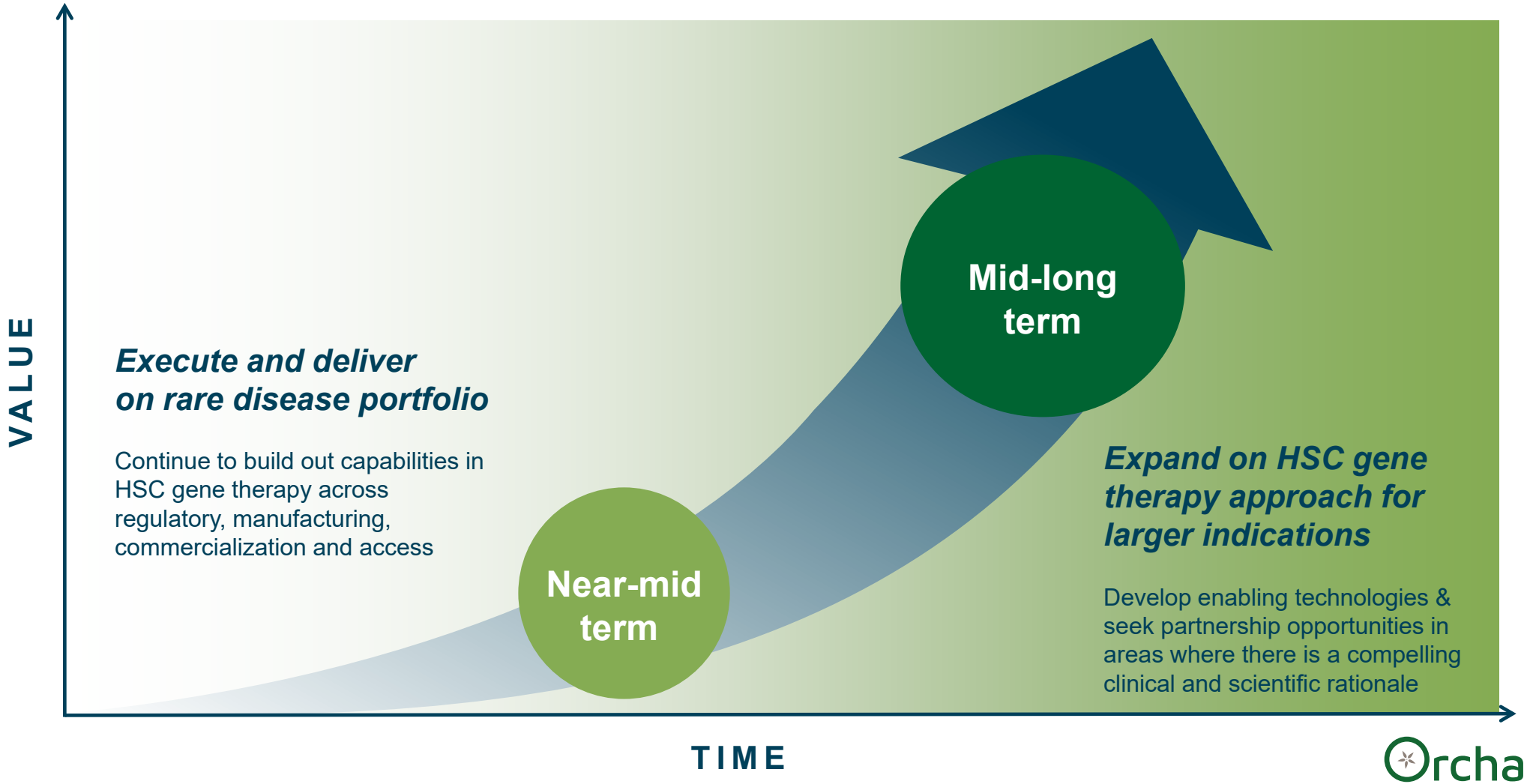
Certain information set forth in this presentation and in statements made orally during this presentation contains “forward-looking statements”. Except for statements of historical fact, information contained herein constitutes forward-looking statements and may include, but is not limited to, the Company’s expectations regarding: (I) the safety and efficacy of Libmeldy and 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 preclinical and clinical data for its product candidates and the likelihood that such data will be positive and support further development and regulatory approval of these product candidates; (VI) the timing and likelihood of approval of such product candidates by the applicable regulatory authorities; (VII) the adequacy of the Company’s supply chain and ability to commercialize Libmeldy, including the ability to secure adequate pricing and reimbursement to support continued development and commercialization of Libmeldy; (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 and cash equivalents 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 preclinical and 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 quarterly report on Form 10-Q for the quarter end June 30, 2021, as filed with the SEC, 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.

Orchard therapeutics™

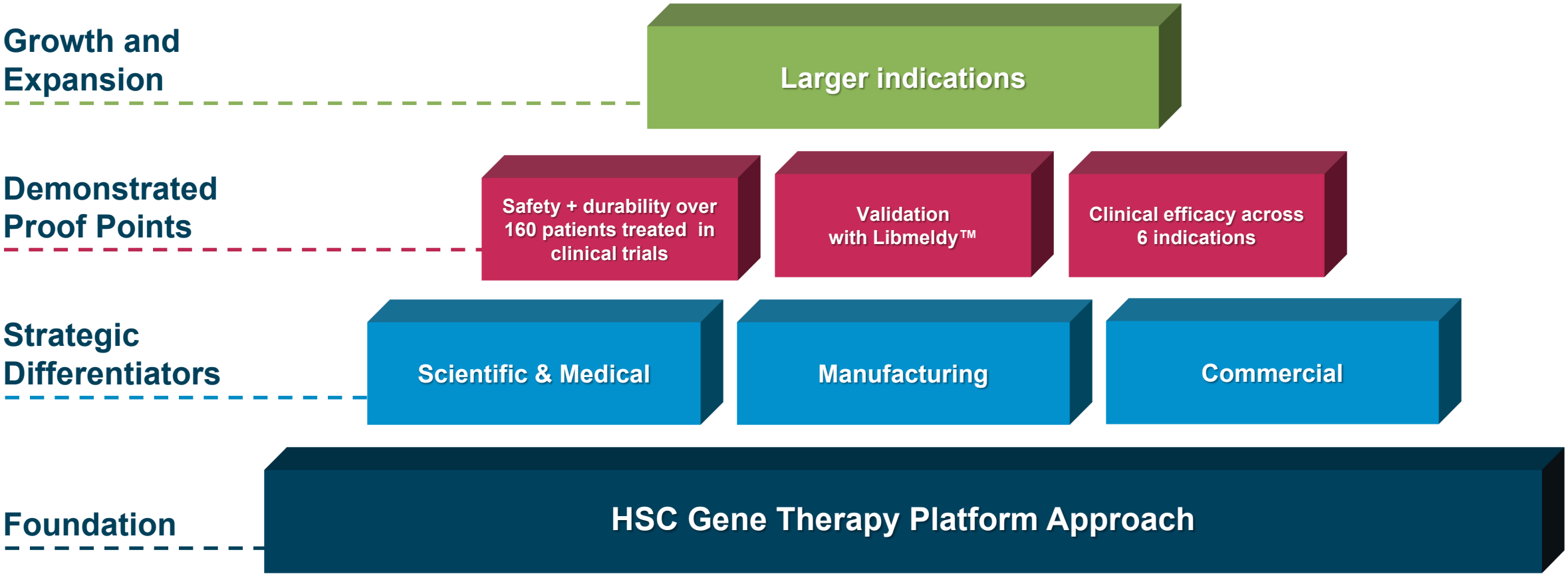
We aspire to end the devastation caused by genetic and other severe diseases through the curative potential of HSC gene therapy.

Accelerating Long-term Growth and Value Creation By Expanding into Larger Indications



Orchard therapeutics

We Are Delivering Now and Building for the Future



- Libmeldy™ (atidarsagene autotemcel) was approved by the European Commission in December 2020
- Data based on in-house data as of February 2021 and comprises all patients treated with CD34+ hematopoietic stem cells transduced *ex vivo* with vector of interest, inclusive of current and former programs.

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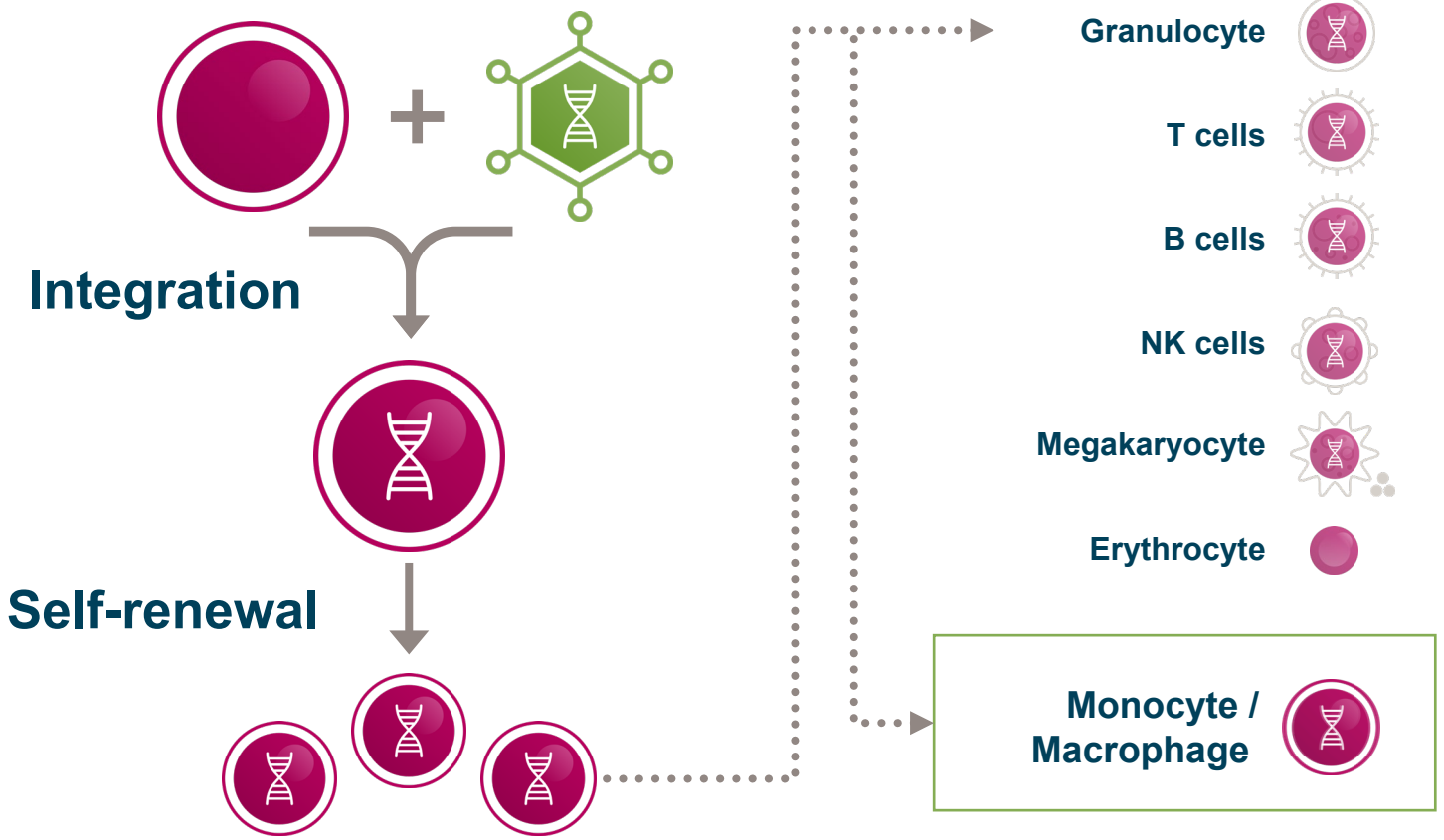
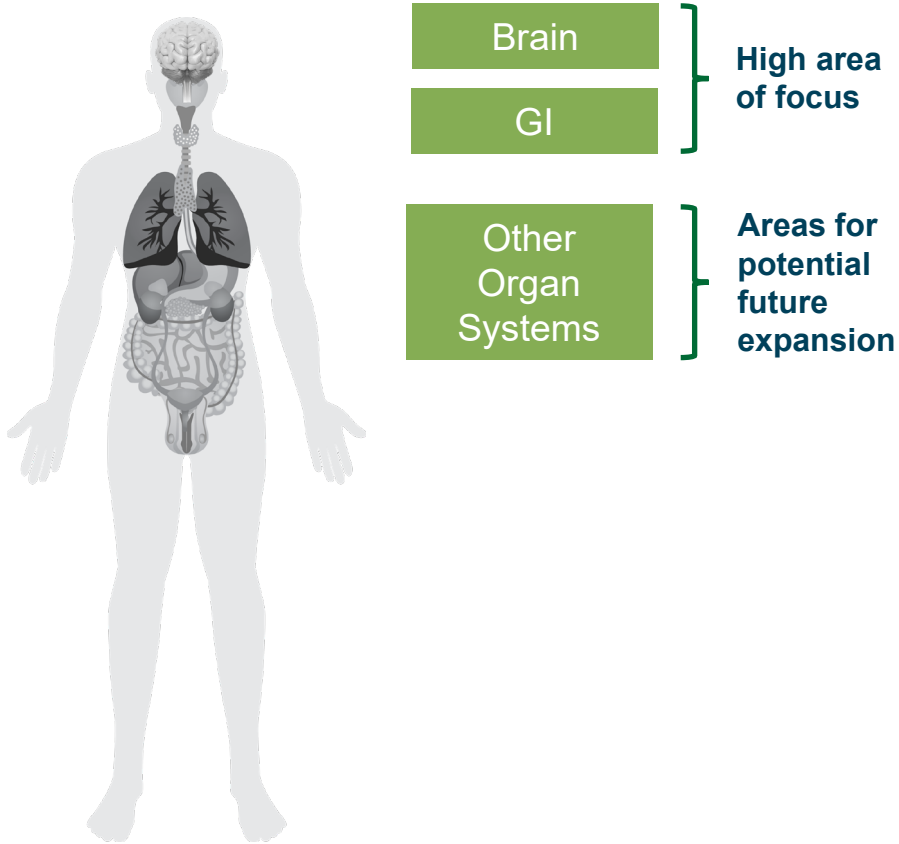
HSC Gene Therapy Offers a Highly Differentiated Approach





Literature references: Alessia Capotondo, Rita Milazzo, Letterio Salvatore Politi, Angelo Quattrini, Alessio Palini, Tiziana Plati, Stefania Merella, Alessandro Nonis, Clelia di Serio, Eugenio Montini, Luigi Naldini, and Alessandra Biffi, PNAS September 11, 2012 109 (37) 15018-15023; https://doi.org/10.1073/pnas.1205858109; Tissue macrophages: heterogeneity and functions, Siamon Gordon and Annette Plüddemann, BMC Biology 2017 15:53, 29 June 2017

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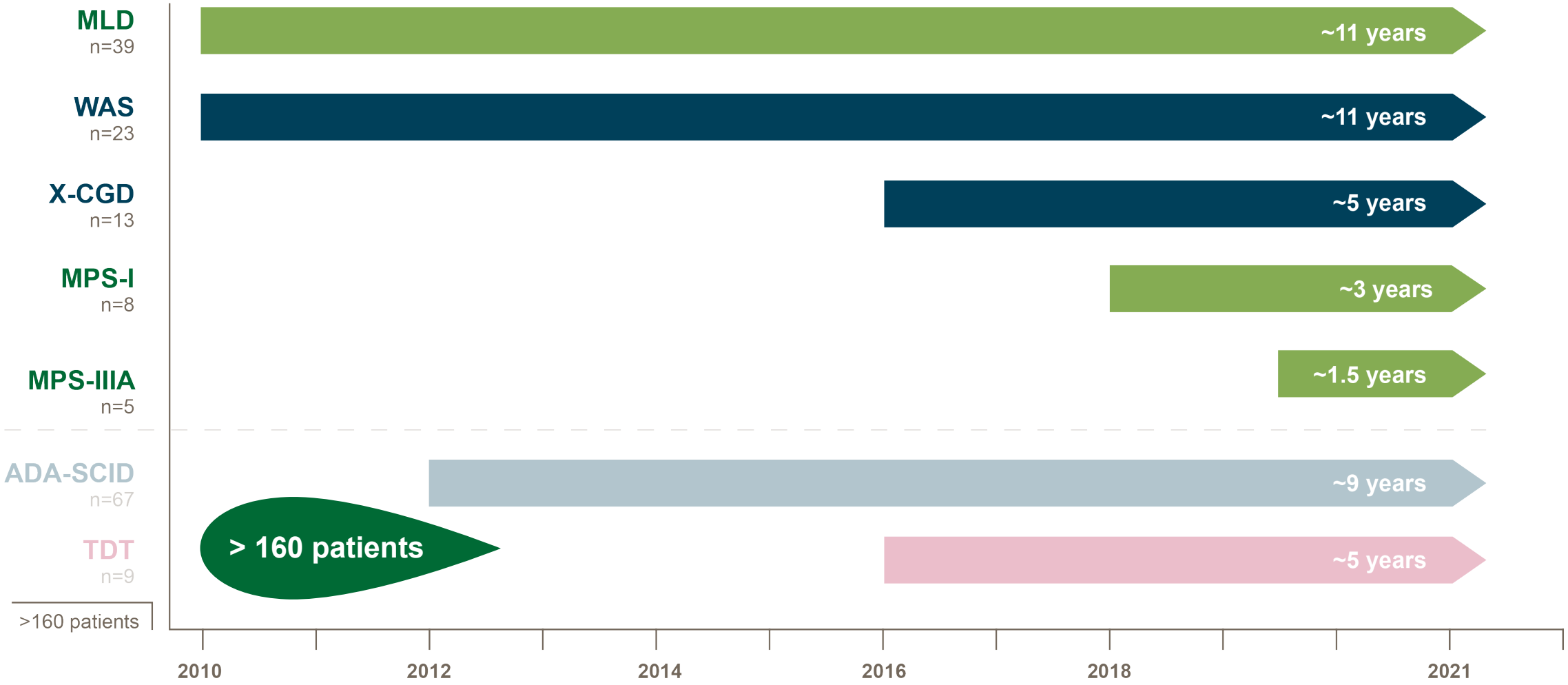
Durability of Response and Safety Demonstrated via Longest Patient Follow-up



- 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).
- Data based on in-house data as of February 2021 and comprises all patients treated with CD34+ hematopoietic stem cells transduced *ex vivo* with vector of interest, inclusive of current and former programs...

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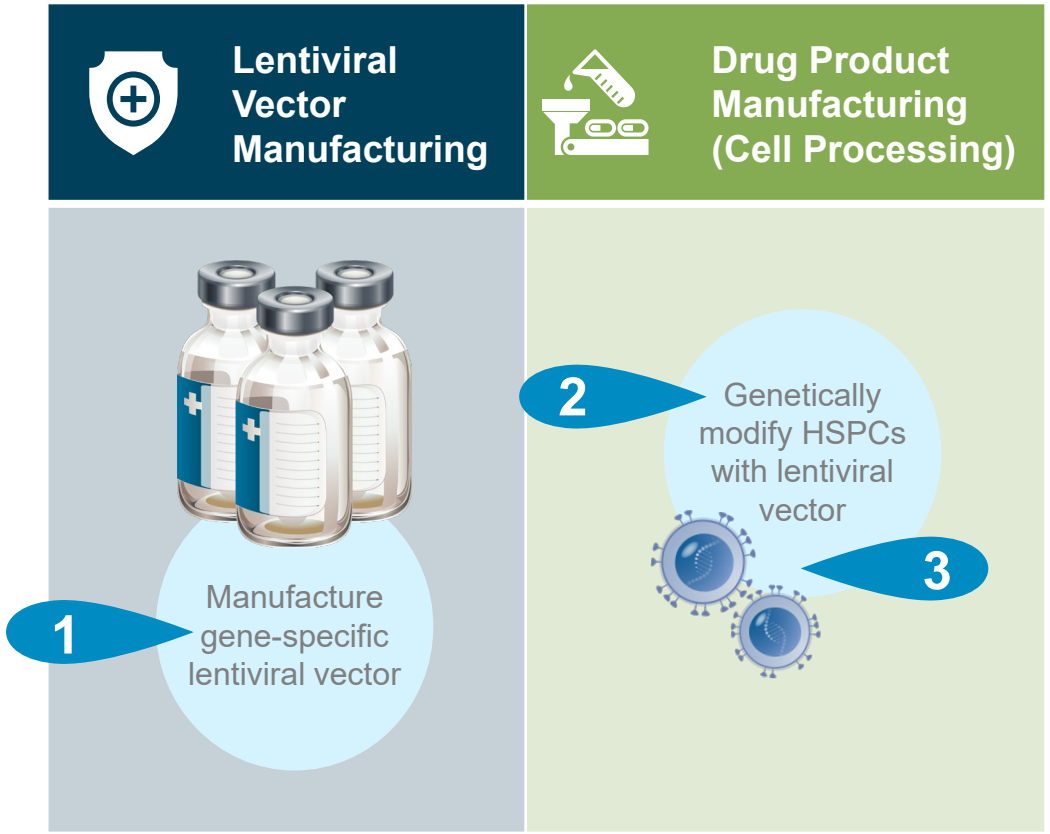
Improving the HSC Gene Therapy Manufacturing Process



		Technology innovations
1	**Vector Production**	**Scalable suspension culture with stable producer cell line**
2	**Stem Cell Transduction**	**Transduction enhancing compounds**
3	**Drug product process**	**Fully closed, automated cell processing**

HSPC = Hematopoietic stem and progenitor cell

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Applying Commercial Strategy to Launch Gene Therapies Globally

Leverage for Libmeldy and future launches

Enable Patient ID & Diagnostics

Multi-pronged diagnostics initiatives and newborn screening in EU and U.S.

Expand Geographic Footprint

Qualifying leading centers with transplant and disease area experience

Establish Global Supply Network

Inventory, capacity and logistics of supply

Secure Market Access

Multi-stakeholder engagement with flexible payment models

Libmeldy™ (atidarsagene autotemcel) was approved by the European Commission in December 2020

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HSC Gene Therapy: Meeting the Need in Severe Neurodegenerative Disorders

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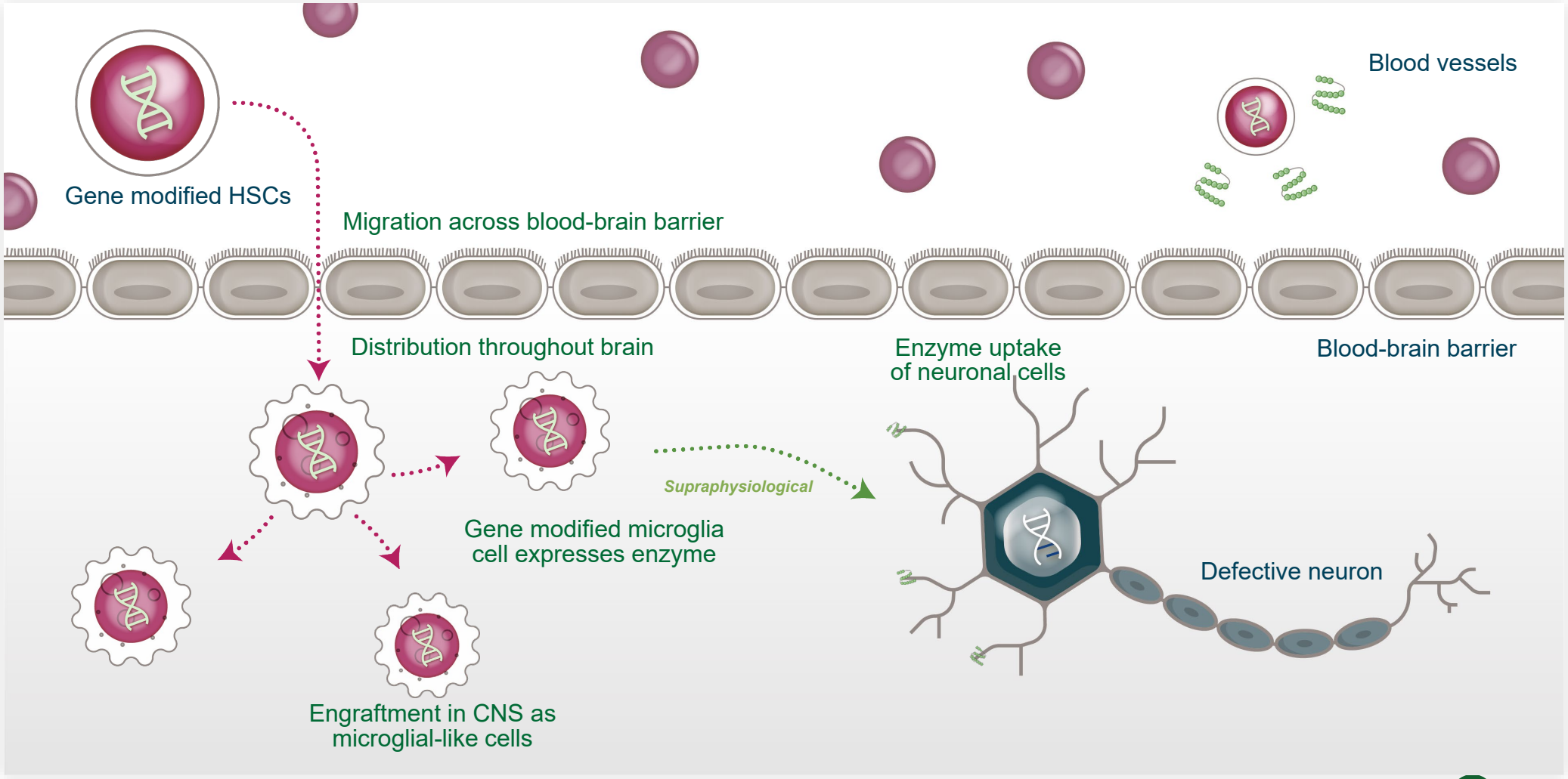
Delivering Proteins to Brain

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



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Growing Body of Patient Data in Neurodegenerative Disorders

Expected Program Milestones

MLD

- Libmeldy™ European launch
- OTL-200 U.S. regulatory feedback received; BLA filing late-2022 to early-2023

MPS-IH

- Parallel scientific advice received for OTL-203 registrational trial
- Finalize design and initiate OTL-203 global registrational study (2022)

MPS-IIIA

- OTL-201 initial enrollment target (5 patients) met in POC study
- Present interim data from OTL-201 POC study (2021 and 2022)

GRN-FTD

Research program preclinical data in 2021

ALS

Research program

Discovery pipeline*

*Other undisclosed development programs

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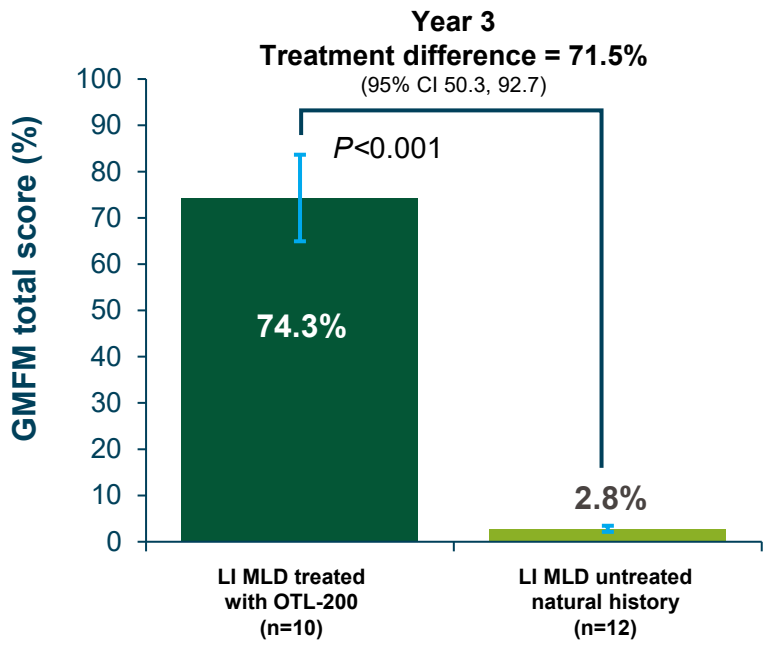
Libmeldy™ (OTL-200) for MLD: Significantly Superior Motor and Cognitive Function Demonstrated vs. Natural History

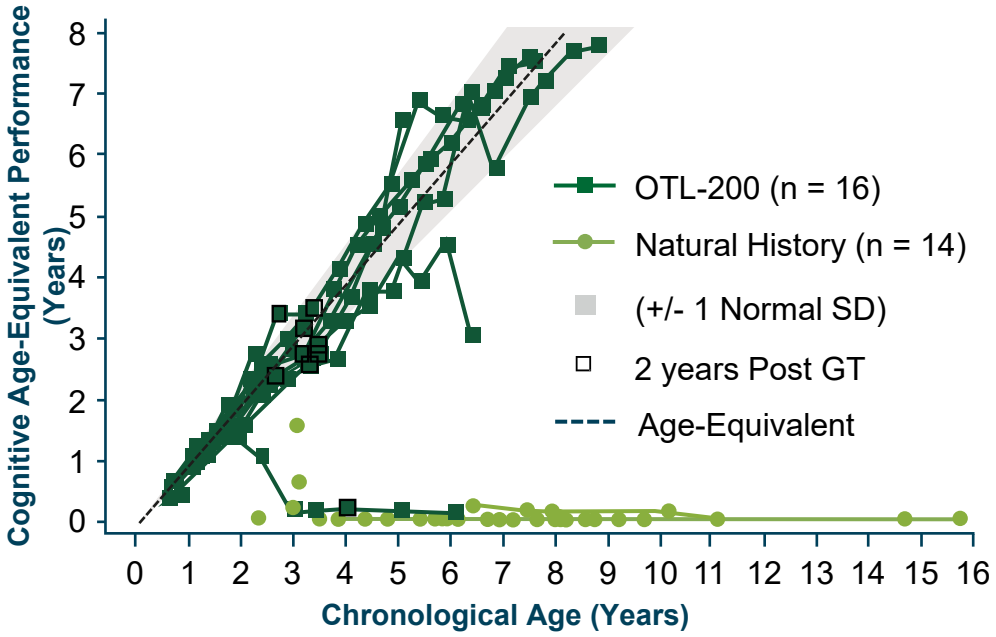
Late Infantile MLD



libmeldy™
(Autologous CD34+ cells encoding ARSA gene)

Approved for early-onset MLD in the EU

Late Infantile MLD



LI, late infantile; EJ, early juvenile CI, confidence interval; GMFM, gross motor function measurement; MLD, metachromatic leukodystrophy;
Both LI and EJ patients (EJ not shown) 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 standard error of the adjusted mean; P-values are from a two-sided 5% hypothesis test with null hypothesis of ≤ 10% difference

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.å

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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MPS-IH: Areas of Significant Unmet Need with Current Standard of Care

Enzyme Replacement Therapy (ERT)	HSCT (allogeneic bone marrow transplant)	HSC Gene Therapy
Limitations		***Potential Differentiation***

• *Limited efficacy* on neurological symptoms and growth (enzyme unable to cross blood brain barrier)
• *No patients* achieved normal urinary GAG levels during confirmatory studies[1]
• *Chronic treatment* = significant burden on healthcare resources
	• *Partially stabilizes* cognitive development (if treated early)
	• *Considerable* residual disease burden in majority of patients[2]
	  ◦ Growth still significantly affected, deviating from reference curves[2]
	  ◦ ***45%*** *moderate to severely impaired* cognitive development at last follow-up[2]
		• Restoration of healthy microglia function (via secretion and cross-correction)
		• Supraphysiological enzyme expression
		• Emerging clinical profile
		• One-time administration + potential for long-term durability

GAG= Glycosaminoglycans
Sources: [1] Aldurazyme prescribing information [2]Aldenhoven (2015): data from 217 MPS-IH patients treated at 10 centres in the US and EU (1985-2011); median follow-up 9.2 years

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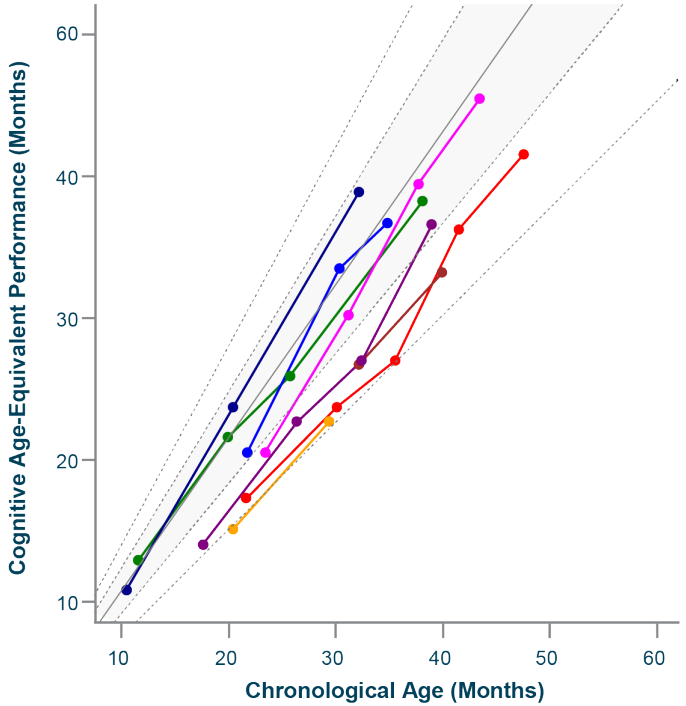
OTL-203 for MPS-IH: Stable Cognitive Function and Growth Within the Normal Range for All Eight Patients

Neurophyschological Tests over Time

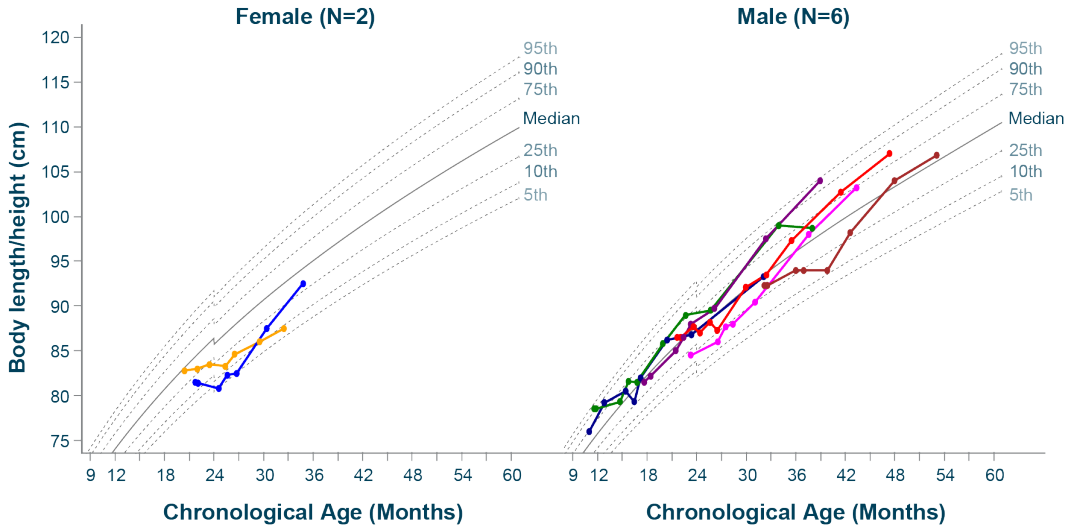
Cognitive Age-Equivalent Score (Overall)



MPSIH001 MPSIH002 MPSIH003 MPSIH004 MPSIH005
MPSIH006 MPSIH007 MPSIH008 Average +/- 1 Normal SD

Improvements in Skeletal Measures

Longitudinal Growth: Normal by Age



MPSIH001 MPSIH002 MPSIH003 MPSIH004
MPSIH005 MPSIH006 MPSIH007 MPSIH008

Note: SD = Standard Deviation; IQ(C) = Intelligence Quotient (Cognition); For Bayley III, the IQ(C) is the cognitive composite score as collected. For WPPSI, the IQ(C) is defined as the performance scales score. For Bayley II: Cognitive Age-Equivalent will be defined as the Mental developmental Age recorded on the CRF. For Bayley III: Cognitive Raw Scores will be compare to the tabulated values in the Bayley III manual to calculate the Cognitive Age-Equivalent. For WPPSI, Age-Equivalent = (IQ*Chronological Age)/100.

Reference: WHO Multicentre Growth Reference Study Group (2006). WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization Growth standards are based on length for 0-24 months and height for > 24 months, resulting in a jump in the reference curve and percentile ranges at 24 months

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HSC Gene Therapy Is Highly Suited for GRN-FTD: a Large and Growing Opportunity

THE OPPORTUNITY

OTL-204 for GRN-FTD

- Haploinsufficiency of progranulin *(GRN)* strongly associated with FTD (~5% of cases)
- Mutation known to have high penetrance
- Up to 2,500 GRN-FTD prevalent patients in U.S. and EU[1-3]
- ~800 new cases U.S. / EU per year[1-3]

OUR UNIQUE POSITIONING

HSC gene therapy has demonstrated potential to treat diseases of the brain

- Ideal for targeting single gene mutations
- Mechanism of CNS gene delivery validated by preclinical and clinical data from MLD, MPS-I, MPS-IIIA
- Gene-modified HSCs enable delivery of *GRN* to brain

Knopman DS, Roberts RO. *J Mol Neurosci*. 2011, Onyike CU, Diehl-Schmid J. *Int Rev Psychiatry*. 2013 and Riedl L, et al *Neuropsychiatr Dis Treat*. 2014

HSC Gene Therapy: Advancing the Treatment Landscape in Immunological Disorders

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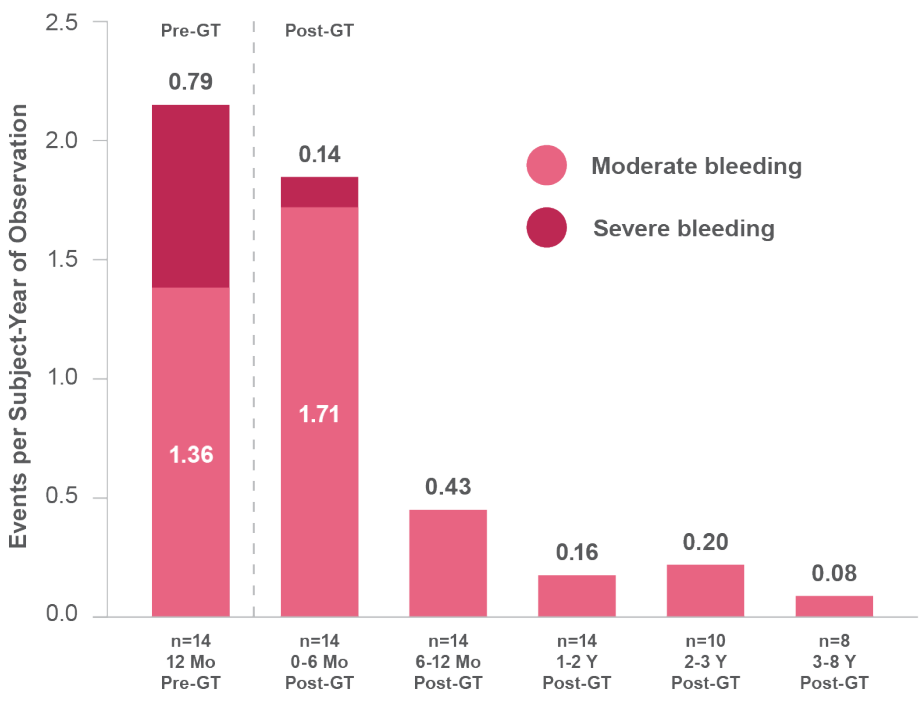
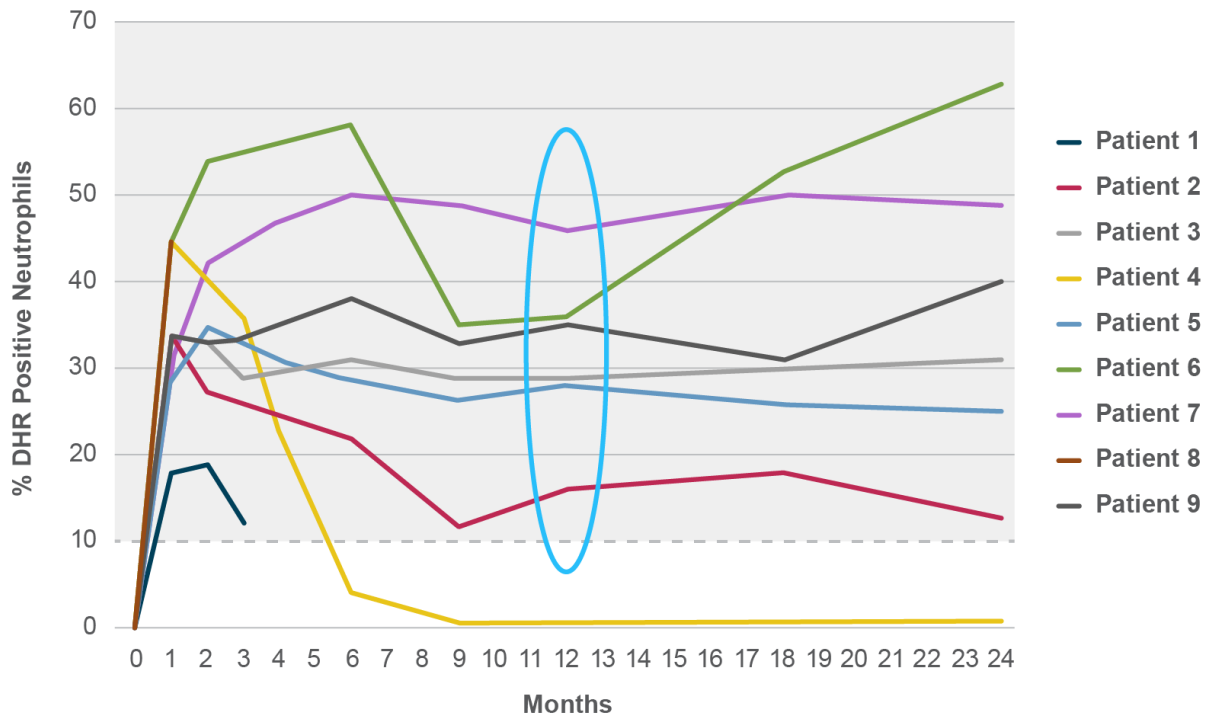
Compelling Evidence in Immunological Disorders

OTL-103 for WAS
Moderate or severe bleeds



Elimination of severe bleeds

OTL-102 for X-CGD
Oxidase Activity



Functional neutrophils (above 10%) in 6 of 7 patients

Data presented at ASH 2019
Events per patient-year of observation for each observation period; GT, gene therapy; mo, months, N, number of patients; Y, years

Data published January 2020 in Nature Medicine
† patient deceased from advanced disease; Excludes data from 1 patient treated with drug product deemed by the investigator to be different from the OTL-102 drug product

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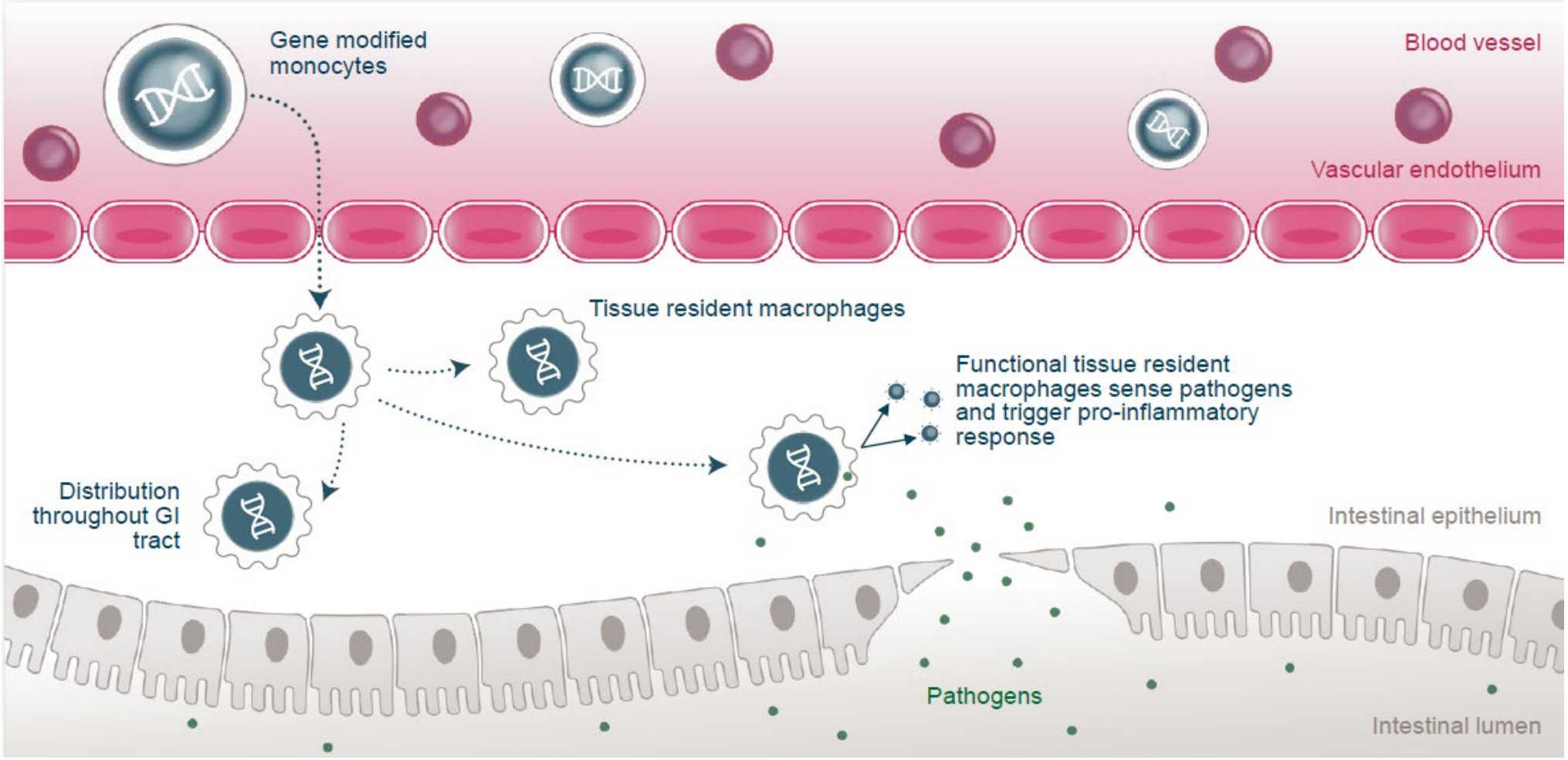
HSC Transplants Give Rise to Tissue Macrophages with the Potential to Reconstitute Functional Gut Innate Immunity



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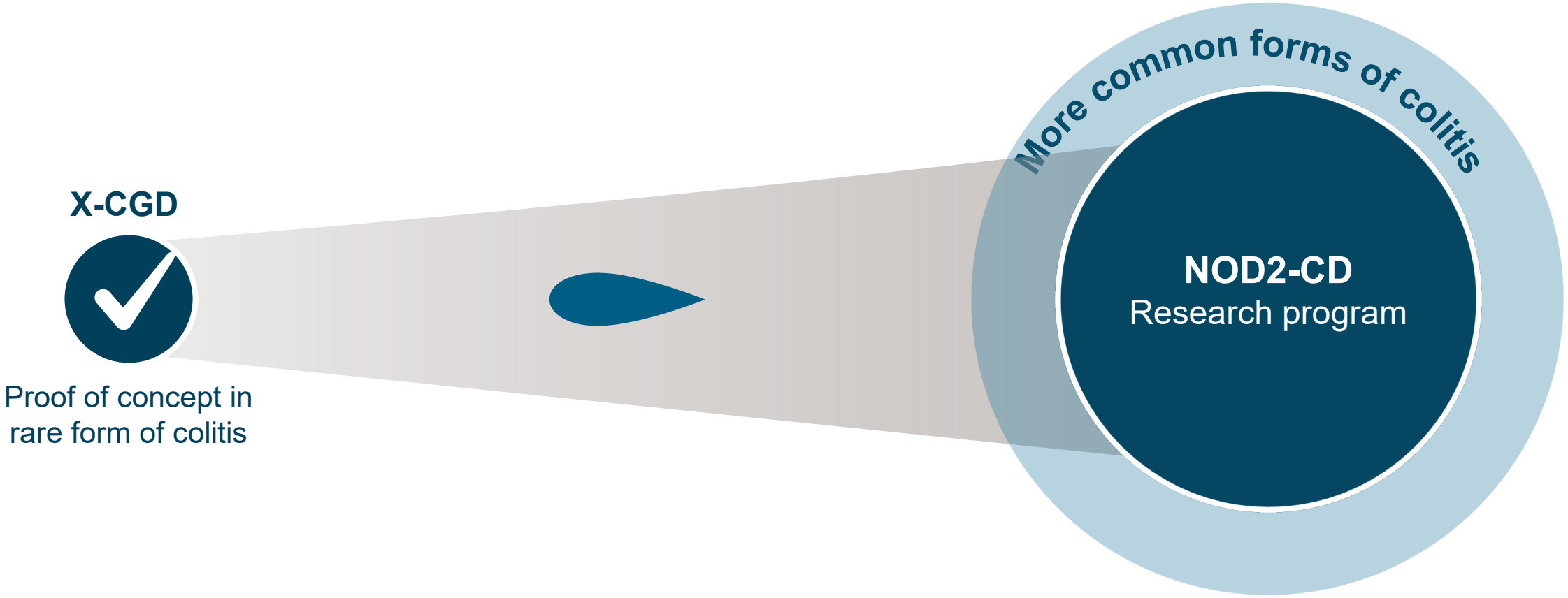
Clinical Validation in X-CGD Supports Application in Larger Populations such as NOD2 Crohn's Disease



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OTL-104 for NOD2-Crohn's Represents a Significant Commercial Opportunity

THE OPPORTUNITY

NOD2-Crohn's

is a significant segment of Crohn's disease

- Up to 200,000 estimated patients with two mutated NOD2 alleles (7-10% of all Crohn's disease) in the U.S. and EU[1,2,3]
- NOD2-CD is increasingly recognized as a monogenic form of CD

OUR UNIQUE POSITIONING

Demonstrated potential of HSC gene therapy to treat other forms of colitis

- HSC GT and HSCT correct colitis in X-CGD + other monogenic PIDs
- NOD2-CD disorder of monocytes / macrophages in GI wall
- NOD2 patients often have severe relapsing disease despite immunosuppressive therapy
- Severe CD already associated with need for autologous HSCT

[1,2] CD prevalence estimates: Centers for Disease Control and Prevention; European Crohn's and Colitis Organisation (ECCO)
[3] NOD2: Ashton, James J et al.Clin Transl Gastroenterol. 2020 Feb

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Operations and Upcoming Milestones

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Today's Roadmap for a Sustainable Future

1	**Maintain Strong Balance Sheet**	• Runway into 1H 2023 • Access equity markets following inflection points • Supplement with non-dilutive capital
2	**Invest for Growth**	• Focus on highest value programs • Allocate R&D capital for larger indications • Stage investments in additional rare disease programs
3	**Leverage Partnership Opportunities**	• Evaluate based on disease expertise and commercial footprint • Leverage HSC GT platform as engine for new indications

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Partnership Snapshot

Driving Development of a Best-in-class HAE Gene Therapy

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- Expertise in HSC gene therapy
- Vector development and testing
- Established CDMO network
- Murine transplant studies
- Internal discovery capabilities

+

Pharming

- Extensive clinical and commercial expertise in HAE
- Pre-clinical disease models for HAE
- Capital to fund ongoing development

Together Orchard and Pharming can combine expertise and experience to develop a best-in-class HAE gene therapy to provide the potential for life-long prophylaxis following a single administration

$17.5M	**Up to $189.5M**	**Mid-single to low double-digit**
upfront payment (cash and Pharming equity investment)	in potential milestones	royalties on future sales

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Progress in 2021 Positions Next Set of Expected Milestones

Rich Span Across Clinical, Development and Commercialization

	Preclinical	Clinical	Regulatory	Commercial
2021	**OTL-204:** Data from GRN-FTD research program **OTL-104:** Data from NOD2-CD research program	**OTL-203:** Parallel scientific advice for MPS-I registrational trial **OTL-201:** Enrollment in MPS-IIIA POC study **OTL-203 + OTL-201:** Interim data from POC	**OTL-200:** Obtain RMAT designation **OTL-200:** Determine BLA filing strategy for MLD by mid-2021	**Libmeldy / OTL-200:** continue to lay foundation for access, reimbursement and patient identification in Europe
12-18 Months		**OTL-203:** Initiate registrational study for MPS-I in 2022 Interim data from **OTL-201** and **OTL-203** POC studies	**OTL-103:** Submit MAA filing for WAS in 2022 **OTL-200**: BLA for MLD in late-2022 / early-2023	

Building a fully integrated company

Compelling Fundamentals Driving Near and Long-term Growth

- **1x treatment** – HSC gene therapy approach offers curative potential
- **Strong clinical track record** – over 160 patients treated
- **Clinical validation in rare diseases** – increases confidence for larger indications

libmeldy™▼
(Autologous CD34+ cells encoding ARSA gene)

approved for early-onset MLD in Europe

Cash runway into the first half of 2023

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