Orchard therapeutics

Corporate Presentation

September - October 2019

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) execution of the Company’s vision and growth strategy, including with respect to global growth; and (viii) 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 may cause actual performance and financial results in future periods to differ materially from any projections of future performance or result 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 20-F filed with the SEC on March 22, 2019, 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.

Global Fully Integrated Biotech Dedicated to Transforming the Lives of Patients with Rare Diseases Through Innovative Gene Therapies







Singular focus on *ex-vivo* autologous HSC gene therapy for rare diseases

Global Leadership in Gene Therapy for Rare Diseases

Deep pipeline of 6 clinical-stage gene therapies & potential to treat CNS disorders

Over 150 patients treated, with promising clinical data & durable long-term effects

3 submissions for product approvals anticipated by the end of 2021 (MLD, ADA-SCID, WAS)

5 programs with clinical proof of concept or beyond (most recently TDT and X-CGD)

Establishing manufacturing and distribution capabilities to deliver products globally

$423M in cash as of Q2 2019, recent equity financing extends runway into second half of 2021

Deep Pipeline of Gene Therapies with Transformative Potential

	Preclinical	Clinical proof of concept	Registrational trial	Commercialization	Designations
Neurometabolic disorders					
OTL-200	**MLD** (Metachromatic leukodystrophy)				**RPD**
OTL-203	**MPS-I** (Mucopolysaccharidosis type I)				
OTL-201	**MPS-IIIA** (Sanfilippo type A)				**RPD**
OTL-202	**MPS-IIIB** (Sanfilippo type B)				
Primary immune deficiencies					
Strimvelis®	**ADA-SCID** (Adenosine deaminase severe combined immunodeficiency)				**RPD**
OTL-101	**ADA-SCID** (Adenosine deaminase severe combined immunodeficiency)				**RPD; BKT**
OTL-103	**WAS** (Wiskott-Aldrich syndrome)				**RPD; RMAT**
OTL-102	**X-CGD** (X-linked chronic granulomatous disease)				
Hemoglobinopathies					
OTL-300	**TDT** (Transfusion-dependent beta-thalassemia)				**PRIME**

Several additional research and preclinical programs under development

RPD Program with Rare Pediatric Disease Designation; eligible for a Priority Review Voucher

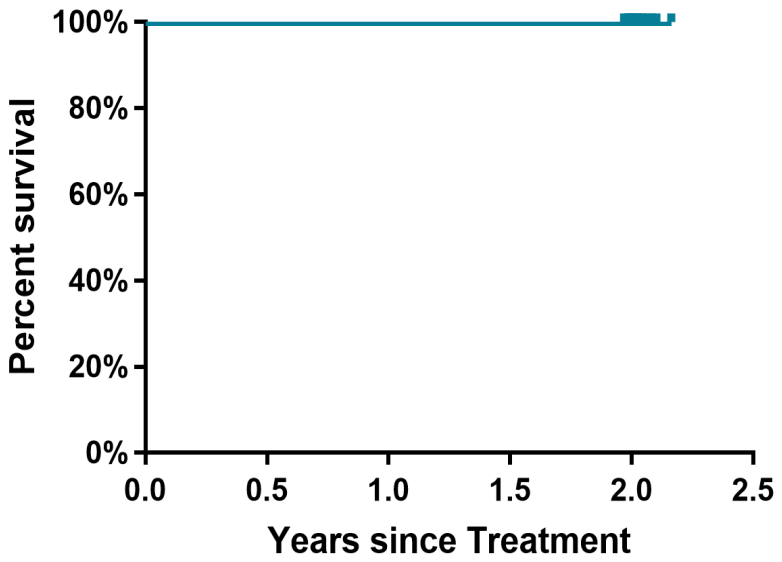
BKT Breakthrough Therapy Designation
PRIME Priority Medicine (PRIME) Designation

Orchard's Lead Programs Show Transformative Potential

Pivotal Data from Three Lead Programs

OTL-101 for ADA SCID

Overall survival data



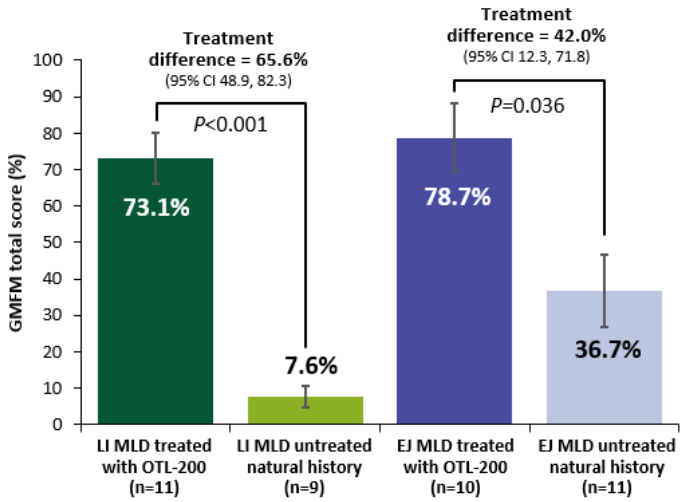
100% overall survival

Source: UCLA study; n=20; American Society for Blood and Marrow Transplantation 2019 presentation

OTL-200 for MLD

Gross motor function measure

Year 2

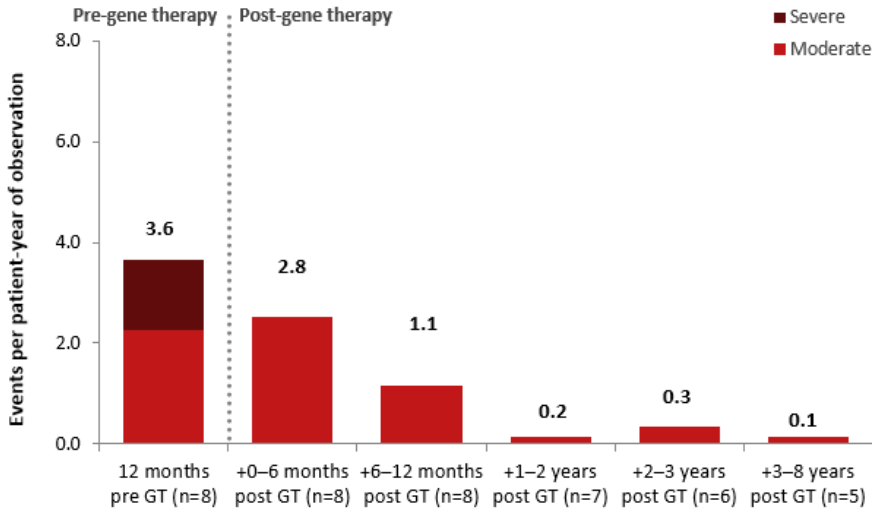


Up to 72% treatment difference vs. natural history

Source: Integrated analysis presented September 4 2019 at SSIEM annual meeting

OTL-103 for WAS

Moderate & severe bleeds



Elimination of severe bleeds

Source: interim clinical study report (CSR) of 10 Jan 2017

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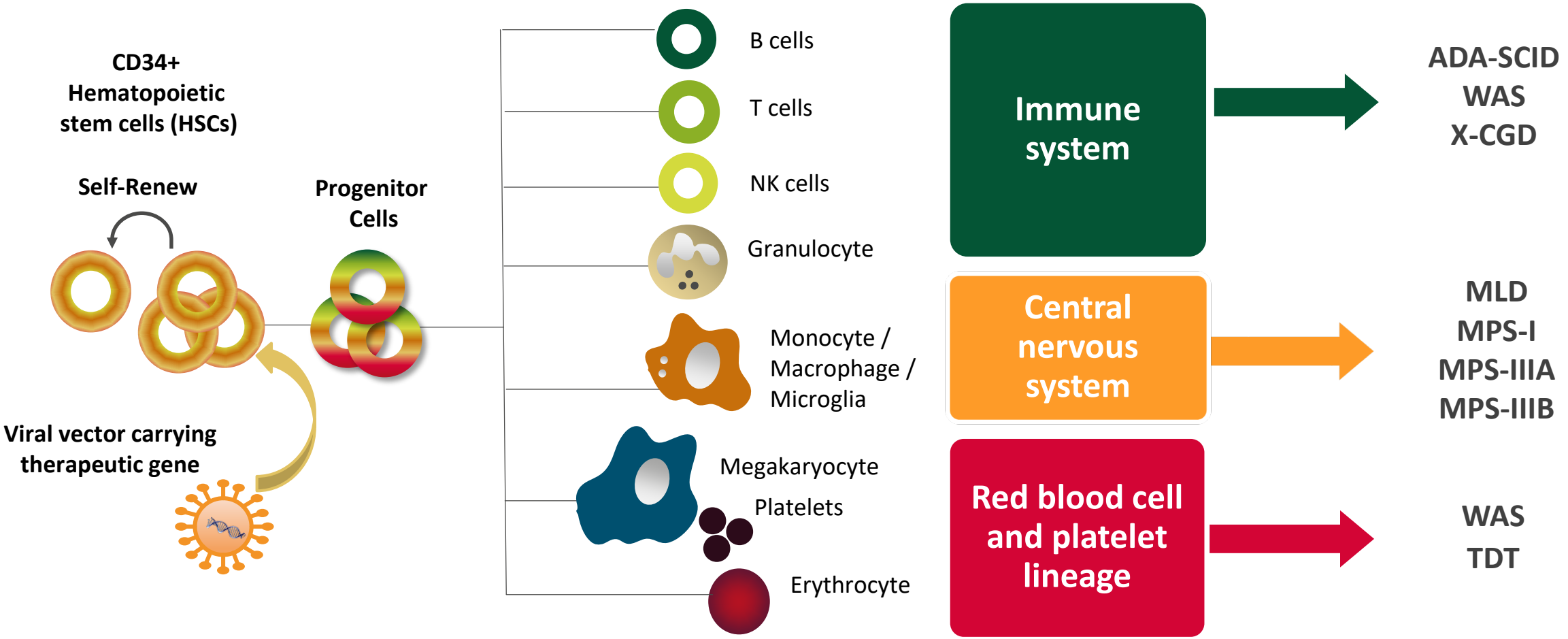
Technology Platform Approach

Delivering Therapeutic Genes for Correction in Multiple Physiological Systems

Hematopoietic stem cells	Mature blood cells	Physiological systems	Current Indications



Potential for sustained disease correction after a single administration via gene-modified HSCs engraftment

Orchard's *Ex Vivo* Autologous HSC Gene Therapy Approach

Blood cell collection:
Blood HSCs and other progenitor cells identified by the CD34+ cell surface marker, are selected and purified by immunomagnetic selection or CD34+ antibodies

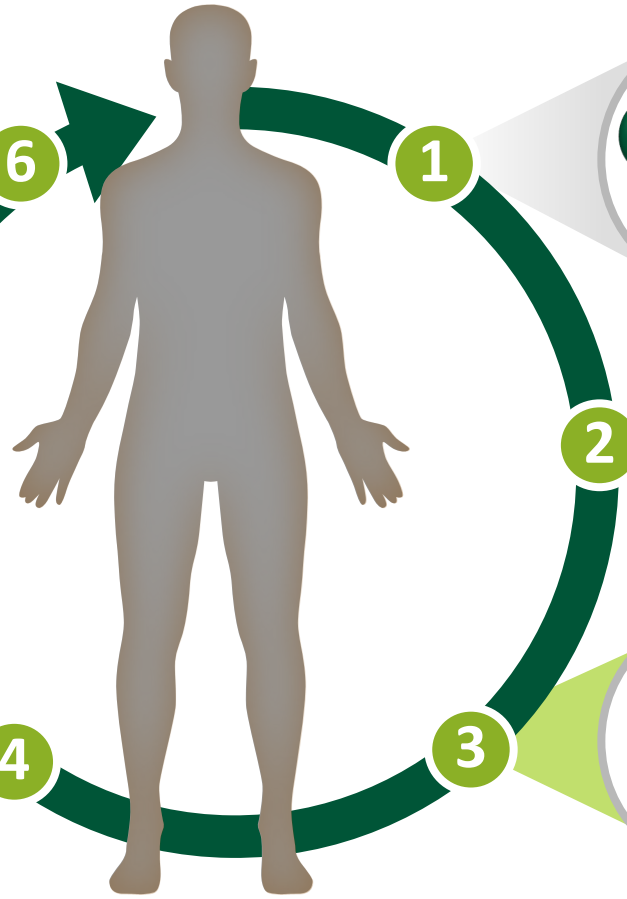
HSC selection and purification:
HSCs, identified by the CD34+ cell surface marker, are selected and purified by magnetic bead selection

Transduction:
HSCs are genetically modified outside of the body (*"ex vivo"*) using a viral vector carrying the functional gene

Cryopreserved genetically modified HSCs

Conditioning:
The patient is conditioned to "make space" for the genetically-modified cells

Administration:
Genetically-modified cells are administered back to the patient



Viral vector carrying the functional gene

1. Corporate Overview presentation, 2Q 2018. http://orchard-tx.com/investors-and-media/events-and-presentations. **2.** Monaco L et al. Presented at: 9th European Conference on Rare Diseases & Orphan Products; Vienna, Austria; 10-12 May 2018. Poster 251.
3. Ferrua F et al. *Hum Gene Ther* 2017;28(11):972-981.

Over 150 Patients Treated with Orchard's Autologous *Ex Vivo* HSC Gene Therapies

Function	Program	Patients treated[1]	Longest patient follow-up (years)
Primary Immune Deficiencies	**Strimvelis®** (ADA-SCID)	24	18
	OTL-101 (ADA-SCID)	62	6
	OTL-103 (WAS)	16	8
	OTL-102 (X-CGD)	10	3
Neurometabolic Disorders	**OTL-200** (MLD)	33	8
	OTL-203 (MPS-I)	6	1
Hemoglobinopathies	**OTL-300** (TDT)	9	3

Persistent, long-term effects across five indications with follow-up out to 8 years

[1] 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 the most recent public data presentation for each program
Data include all patients treated with CD34+ hematopoietic stem cells transduced *ex vivo* with vector of interest.

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Neurometabolic Disorders

Delivery of Proteins to the Brain Unlocks Potential to Treat Large Number of Neurometabolic Diseases

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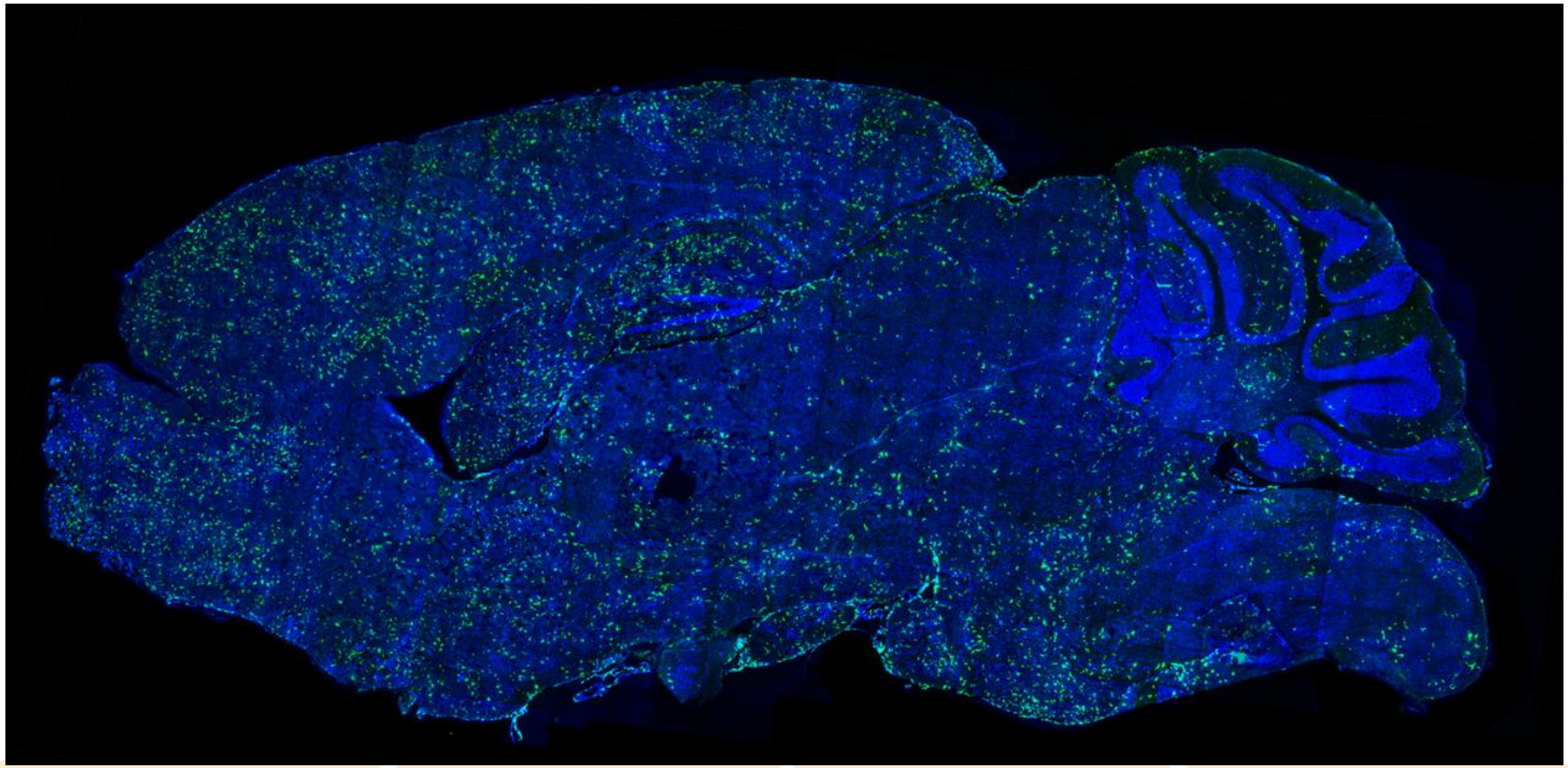
Broad transgene distribution in brain of mouse after administration of HSCs transduced with GFP-encoding vector



MLD | **MPS-I** | **MPS-IIIA** | **MPS-IIIB**

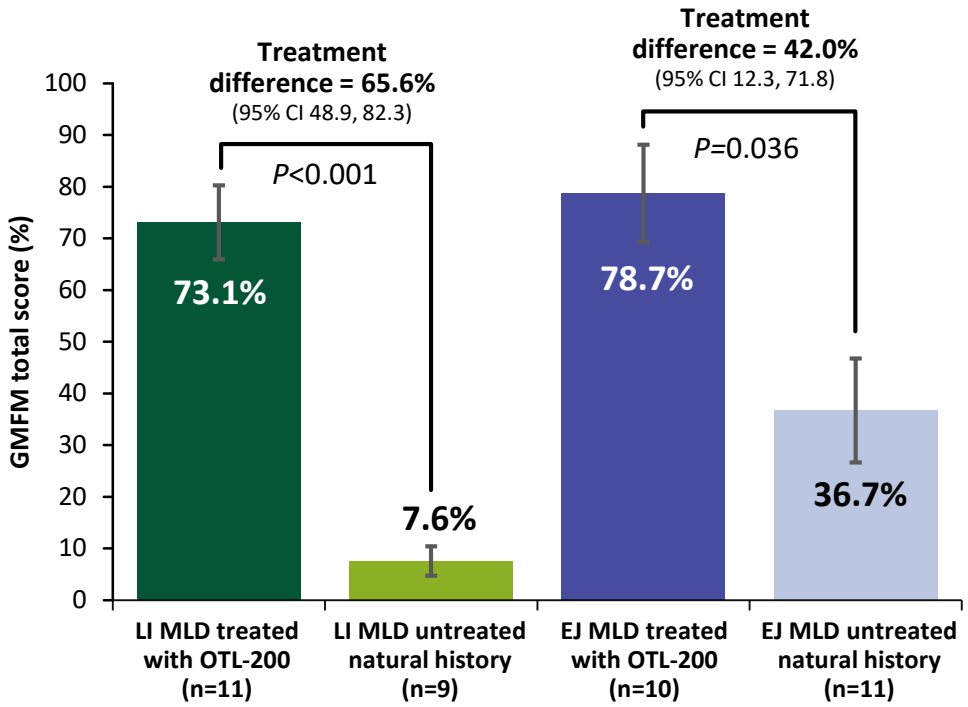
Multiple potential additional neurometabolic indications

Source: Capotondo et al. PNAS 2012;109:15018-15023; Brain of a wildtype mouse transplanted with GFP-LV transduced HSCs after Busulfan conditioning
Green = GFP (green fluorescent protein); **blue** = nuclei staining

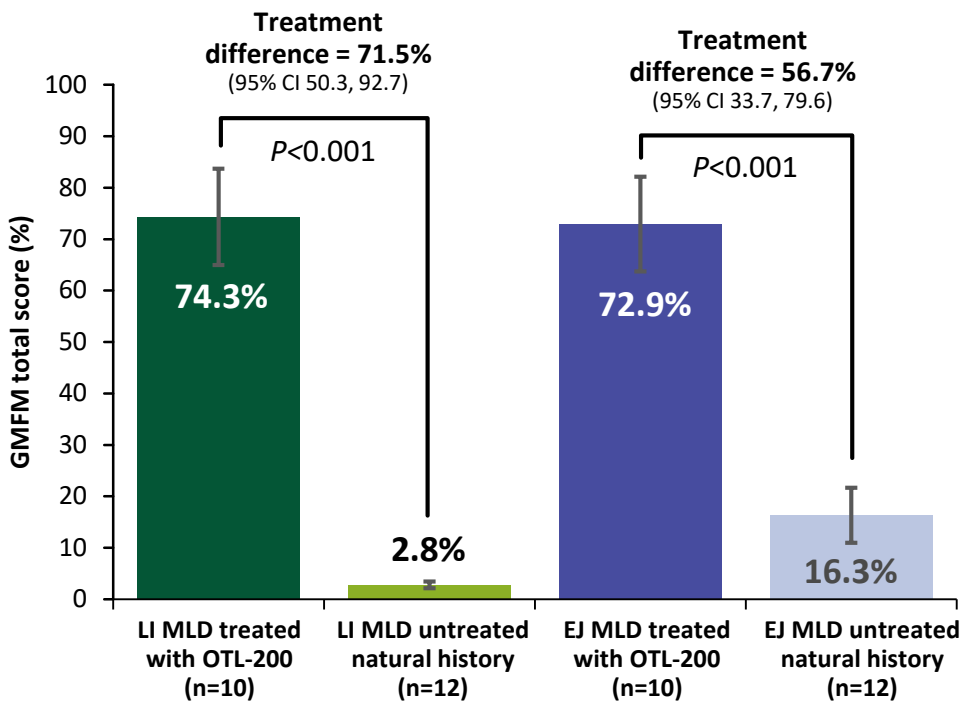
OTL-200 for MLD: Significant Improvements in Motor Function at Two and Three Years Post-Treatment Demonstrate Sustained Clinical Benefit

Results from 29 Patient Integrated Analysis Presented at SSIEM

Year 2



Year 3



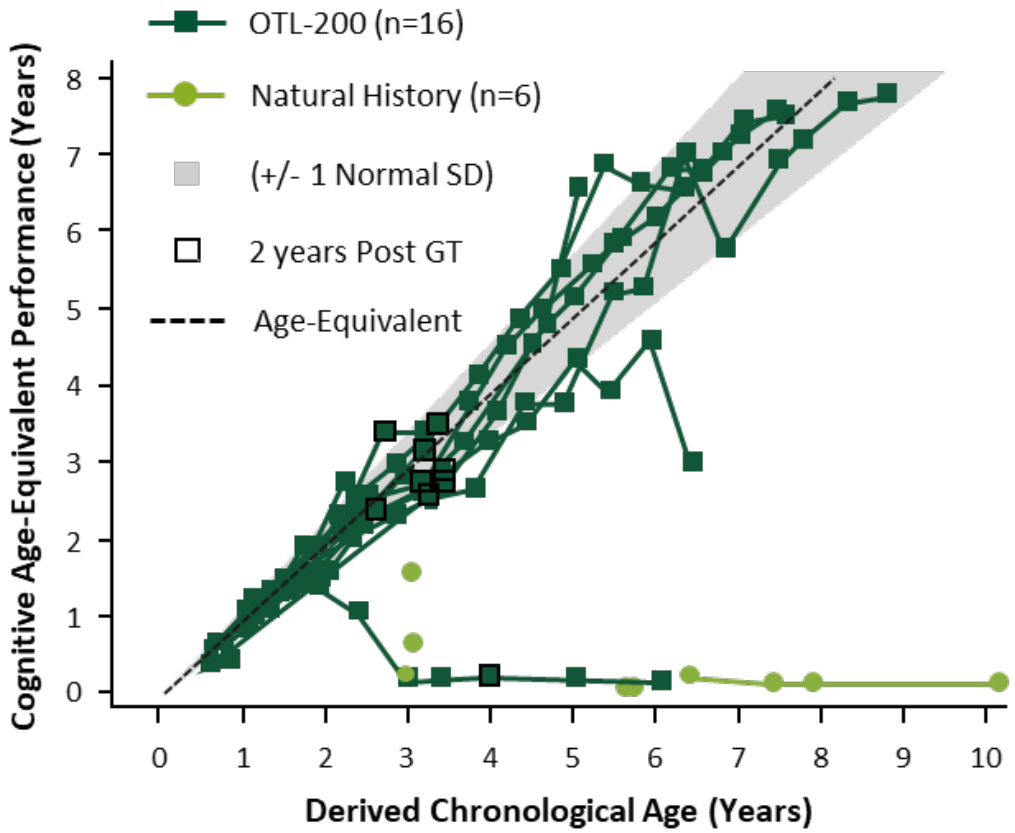
Up to 72% treatment difference in late infantile patients
57% treatment difference in early juvenile patients

Integrated analysis presented September 4 2019 at SSIEM annual meeting
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

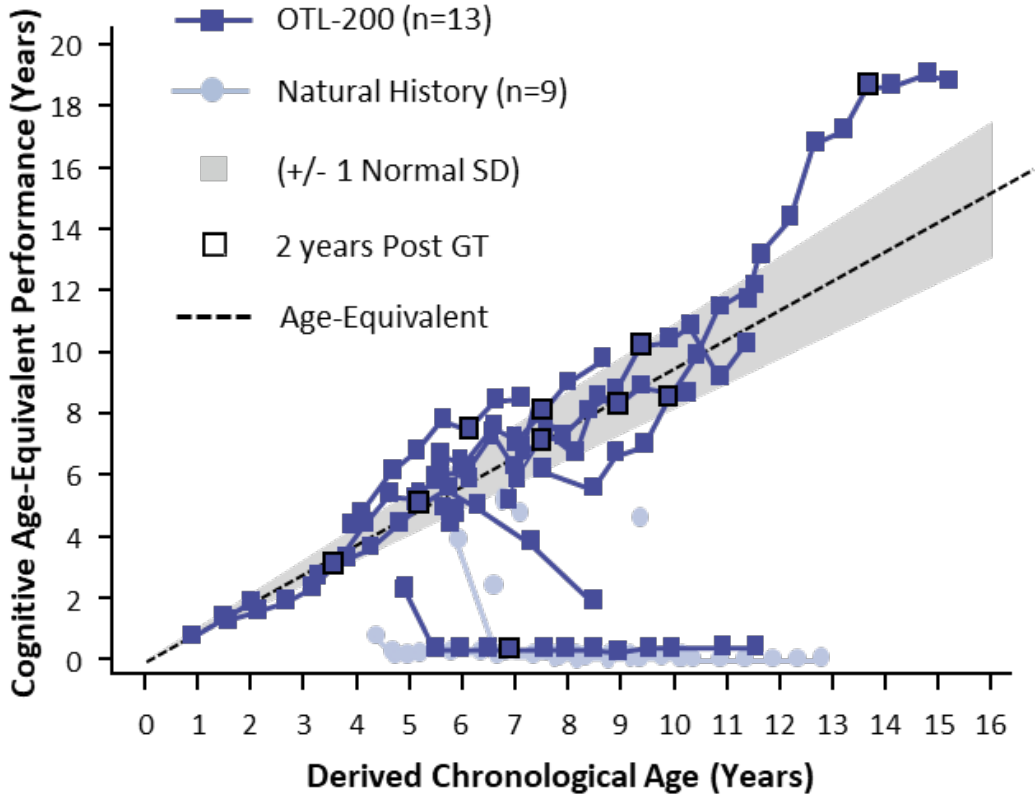
OTL-200 for MLD: Cognitive Performance as Measured by Age Equivalent Scores in the Normal Range for Most Patients Post-Gene Therapy

Results from 29 Patient Integrated Analysis Presented at SSIEM

Late Infantile



Early Juvenile



Integrated analysis presented September 4 2019 at SSIEM annual meeting

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.

OTL-203 for MPS-I: Highly Debilitating Condition Impacting Cognitive, Cardiovascular and Skeletal Function

Disease

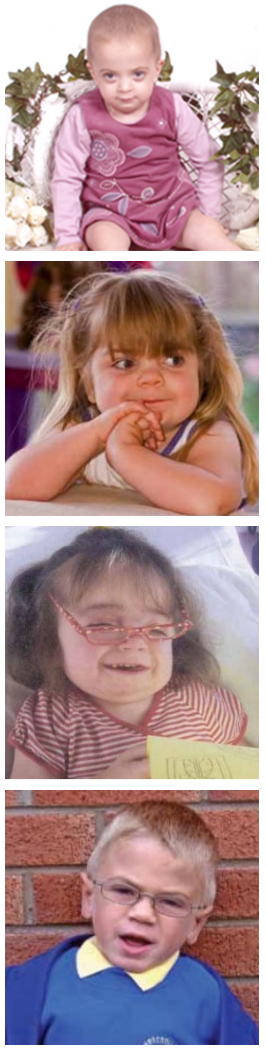
- Autosomal recessive inheritance
- Deficiency of IDUA enzyme leads to accumulation of heparan sulfate
- Severe behavioral defects as well as extensive somatic pathologies
  - E.g. skeletal dysplasia, cardiomyopathy, corneal clouding and hydrocephalus
- MPS-IH (Hurler syndrome) represents the most severe phenotype

Epidemiology

- Incidence is estimated at ~1 in 100,000 live births
- Hurler syndrome accounts for 60% of MPS-I

Current Treatment Options

- Hematopoietic stem cell transplantation (HSCT): treatment of choice for <2.5 years of age
  - Can prolong survival, partially preserve neurocognition and ameliorate some somatic features
  - Should be given before developmental deterioration begins
- Enzyme replacement therapy (ERT)
  - Early use shown to improve some clinical features in less severe / non-Hurler forms of the disease
  - Limited efficacy on neurological symptoms



OTL-203 for MPS-I: Encouraging Preliminary Data from Clinical Proof of Concept Study

Goal to complete enrollment first half 2020 with 1 year follow-up data available in 2021

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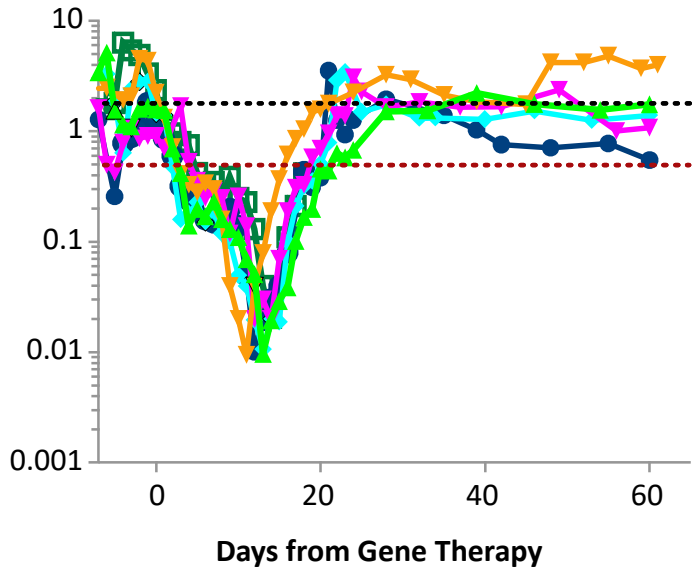
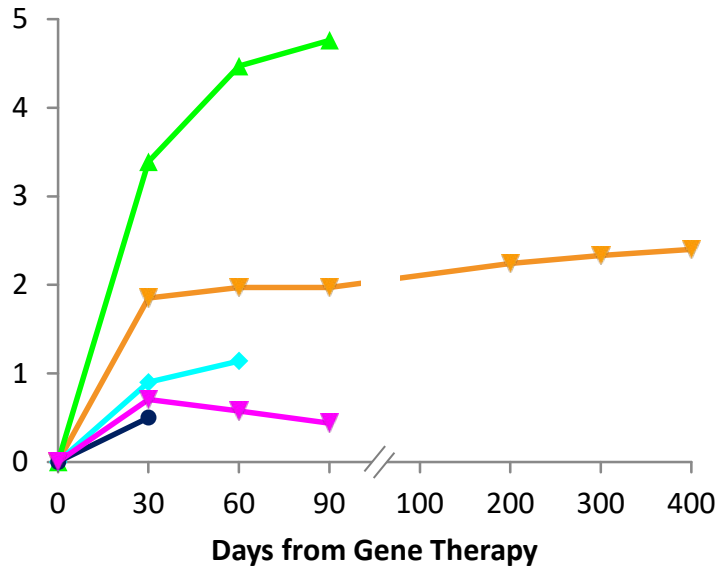
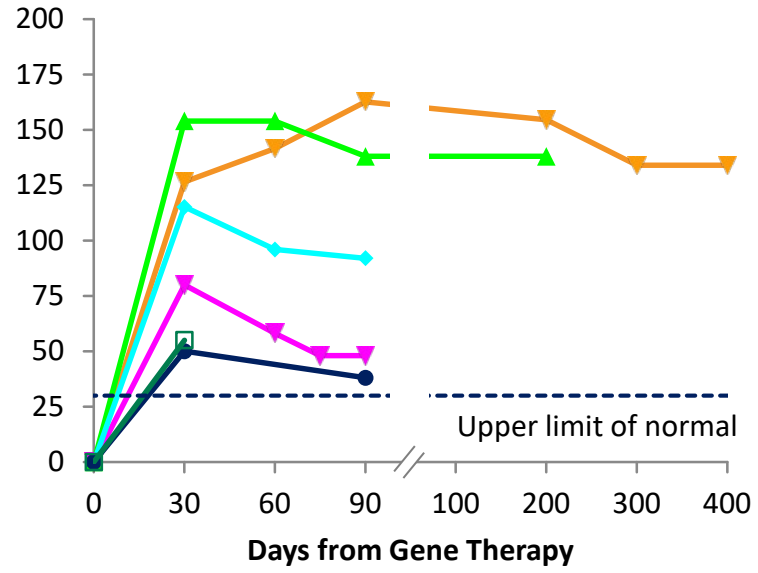
Neutrophils (per nl)



VCN in CD15



IDUA Activity (µmol/L/h)

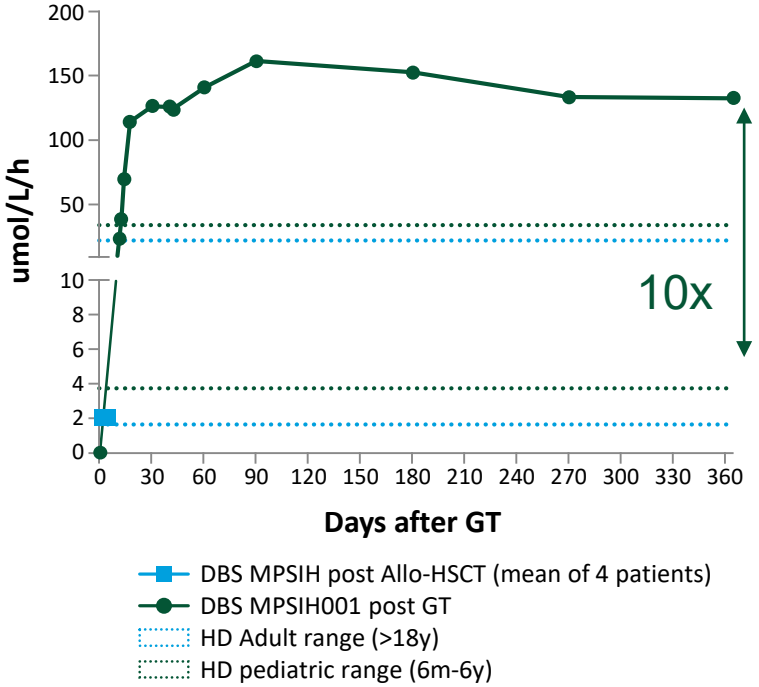


MPSIH001 MPSIH002 MPSIH003 MPSIH004 MPSIH005 MPSIH006

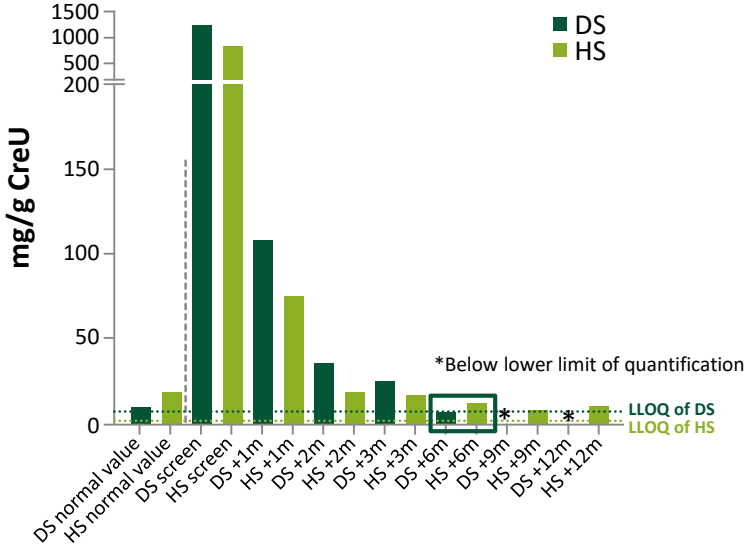
Data presented September 4, 2019 at SSIEM annual meeting

OTL-203 for MPS-I: Encouraging Preliminary Clinical Biomarker Data in Patient with 1 Year of Follow-up

DBS HSC-GT vs DBS Allo-HSCT_MPSIH001

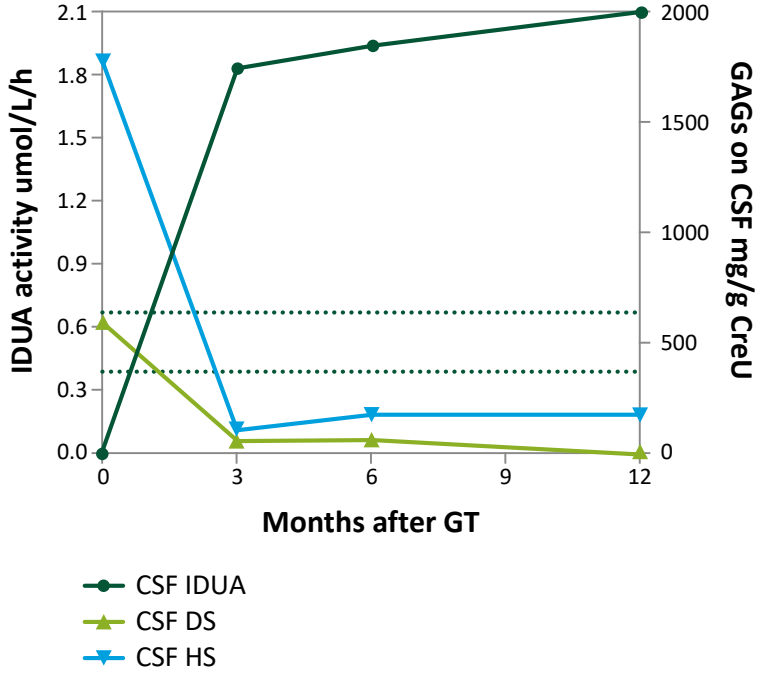


DS and HS in Urine_MPSIH001



Performed at Meyer Hospital, La Marca's Lab

IDUA Activity on CSF vs GAGs on CSF-MPSIH001



Supranormal IDUA enzyme expression in periphery

Rapid metabolic correction of GAG levels in urine and cerebrospinal fluid

Range values DBS calculated on 206 healthy donors (HD) (6 months-6yrs.)
Allo-HSCT IDUA by DBS on 4 pts: mean 2.25, range 1.7-2.9
(Courtesy of R. Parini, S. Gasperini, A. Rovelli, San Gerardo H, Monza)

Data presented September 4, 2019 at SSIEM annual meeting

DBS = dried blood spot
IDUA = Alpha-L-iduronidase
HS= Heparan sulfate

CFS = cerebrospinal fluid
GAGs = glycosaminoglycans
DS= Dehydroepiandrosterone sulfate

OTL-201 and OTL-202 (MPS-IIIA and MPS-IIIB): Preclinical Proof of Concept

MPS-IIIA CTA submission and clinical trial initiation expected in 2019

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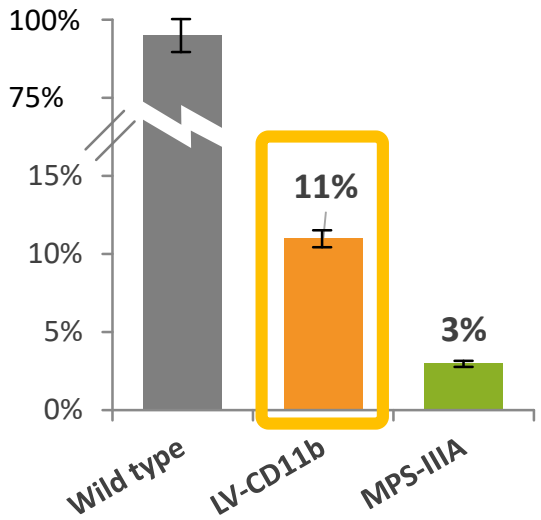
Increased Enzyme Expression in the Brain

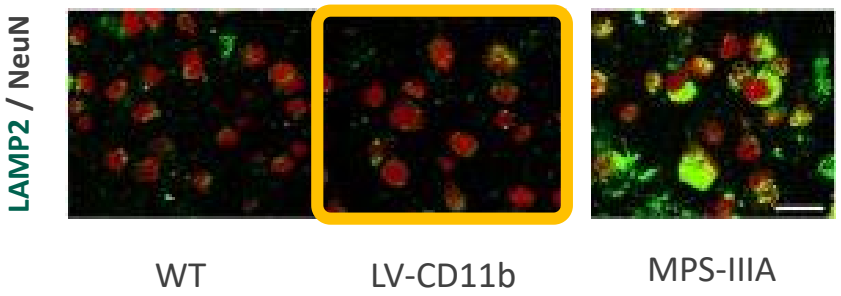
Percentage enzyme vs. wild type



11% enzyme expression vs. wild type

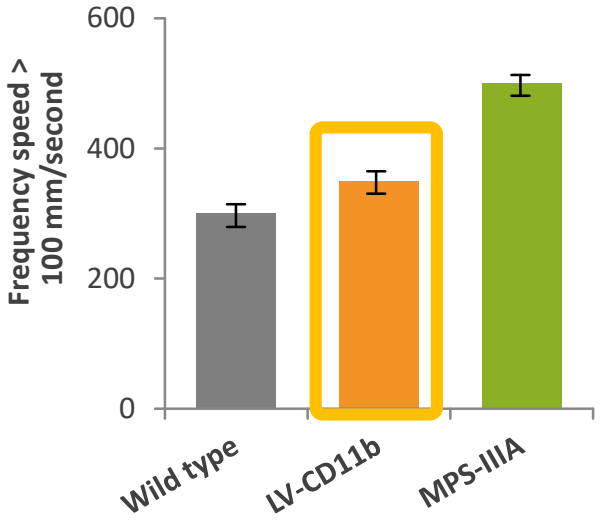
Decreased Substrate Accumulation in the Brain

Staining of neurons and lysosomes



~80% decrease in heparan sulfate vs. MPS-IIIA wild type

Full Behavioral Correction to Wild Type Levels



Reduced hyperactivity

Sergijenko et al, Mol. Ther. 2013, 21(10), 1938-1949

LV:CD11b - self-inactivating (SIN) LV with a codon optimized GSH transgene driven by the myeloid-specific CD11b promoter

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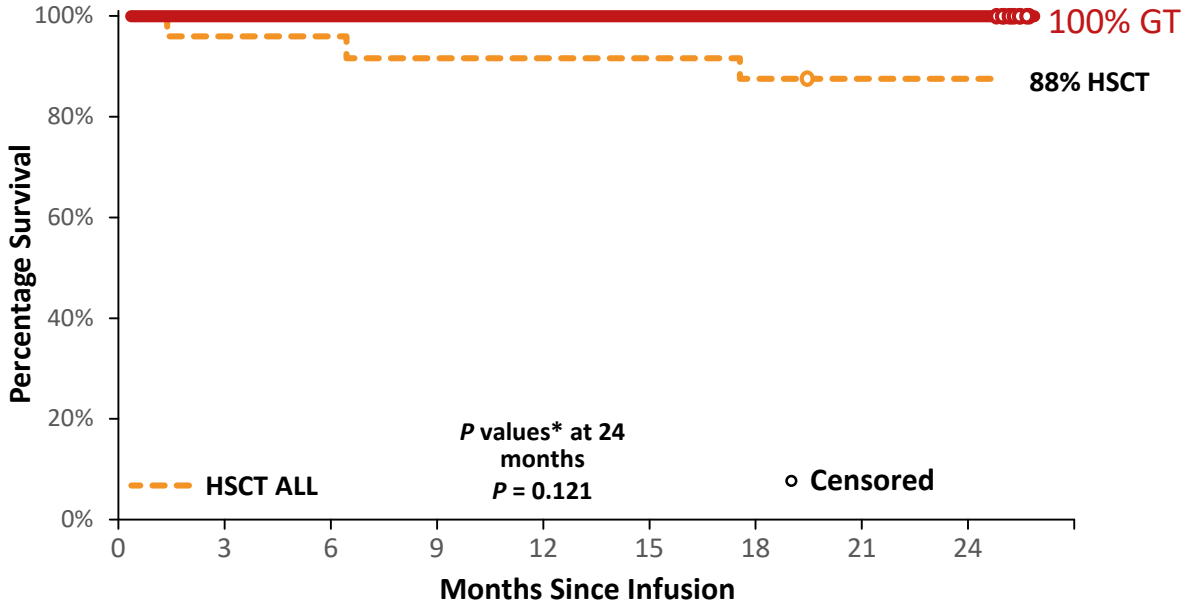
Primary Immune Deficiencies (PIDs)

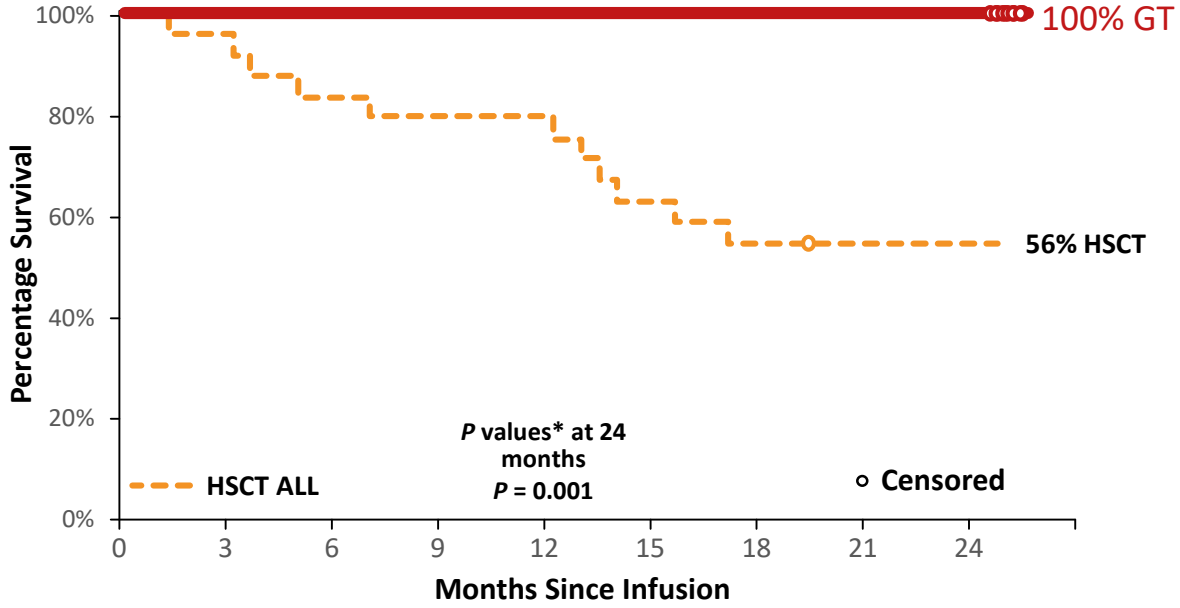
OTL-101 for ADA-SCID: Registrational Trial Supports Transformative Potential

Rolling BLA submission expected to initiate H1 2020 (followed by MAA submission)

Overall Survival



Event-free Survival



100% Overall Survival (n=20)

100% Event-free Survival (n=20)

62 Patients Treated In Total as of December 2018

Up to 6.5 years follow-up

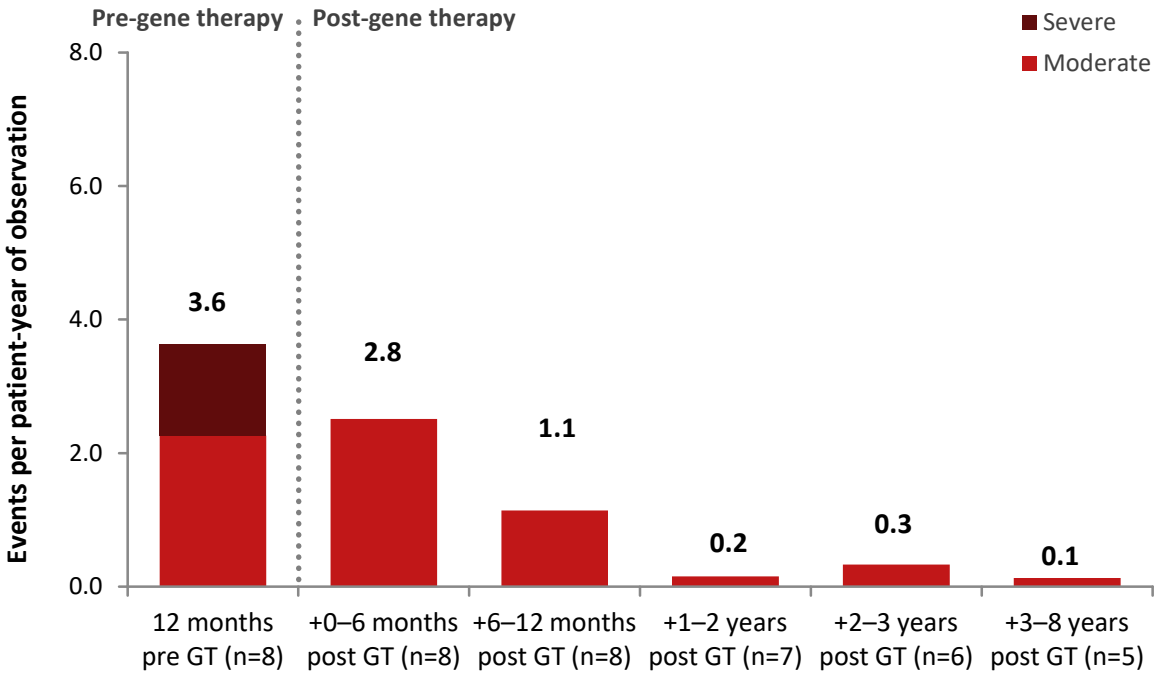
100% overall survival; ~95% event-free survival

Data from registrational 2-year fresh cell product; n=20, presented at ASBMT 2019
*All P values are log-rank tests
One HSCT subject is excluded as they did not complete 24 months of follow-up. Event = survival without an event of reinstitution of PEG-ADA ERT or need for rescue HSCT.

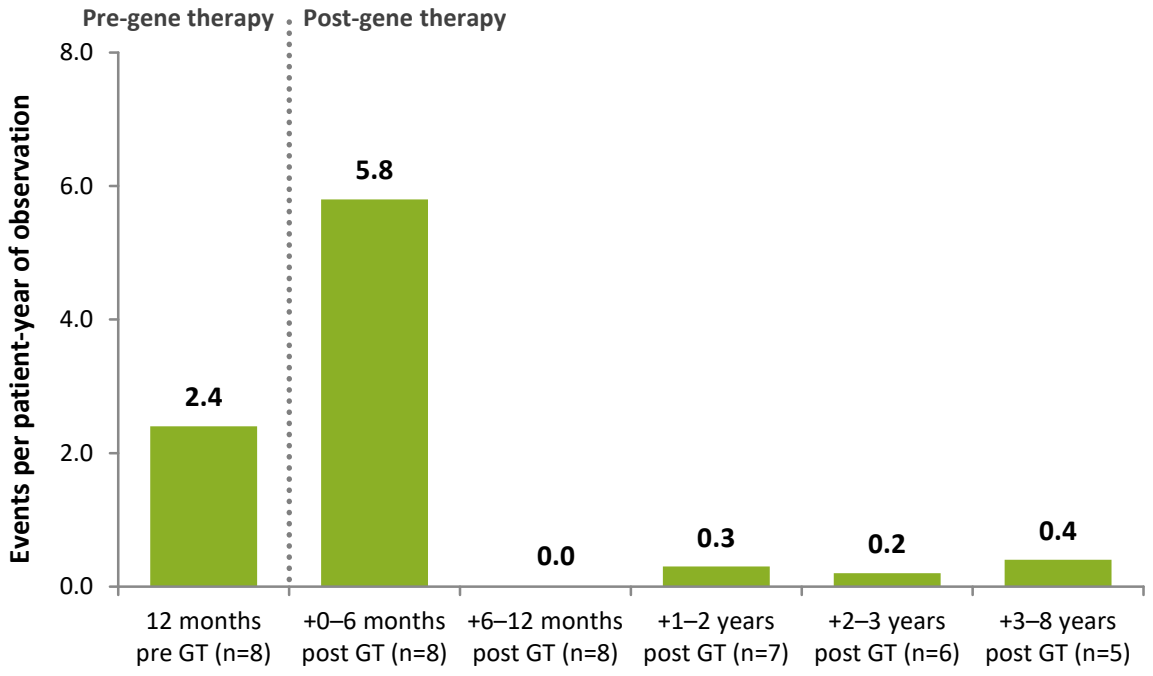
OTL-103 for WAS: Evidence of Consistent and Durable Efficacy

Cryopreserved formulation trial initiated; BLA and MAA submissions expected in 2021

Moderate or severe bleeds per patient per year



Severe infections per patient per year



Elimination of severe bleeds and reduction in the rate of severe infections for patients treated in clinical trials (n=8)

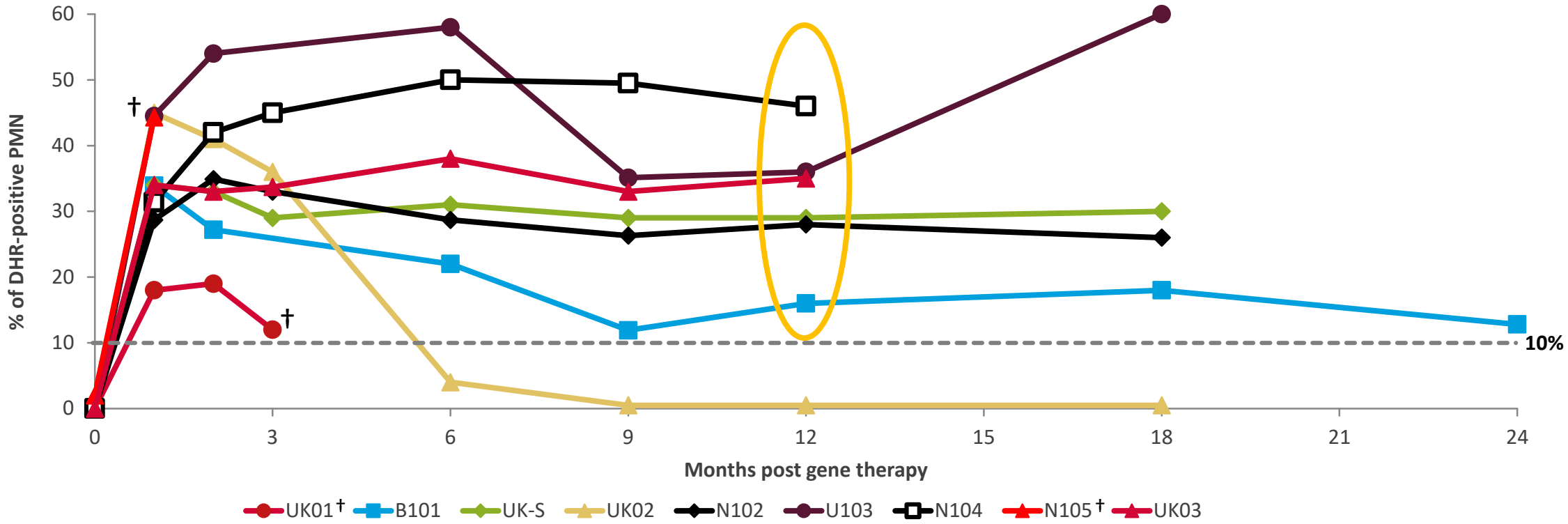
Well-tolerated among 16 patients treated (8 in clinical trials; 8 under compassionate use program)

Data from April 10 2019 Lancet Hematology publication; Events per patient-year of observation for each observation period. Figures reflect data as of the cut-off date of 29 April 2016

OTL-102 for X-CGD: Evidence of Sustained Neutrophil Activity in Patients

Proof of concept established; Designing registrational trial in adults

Oxidase activity – % of DHR-positive peripheral mononuclear cells



Functional neutrophils above 10% at 12 months in 6 patients providing clinical benefit

Data presented at ASH 2018 & ASBMT 2019; † 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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Hemoglobinopathies

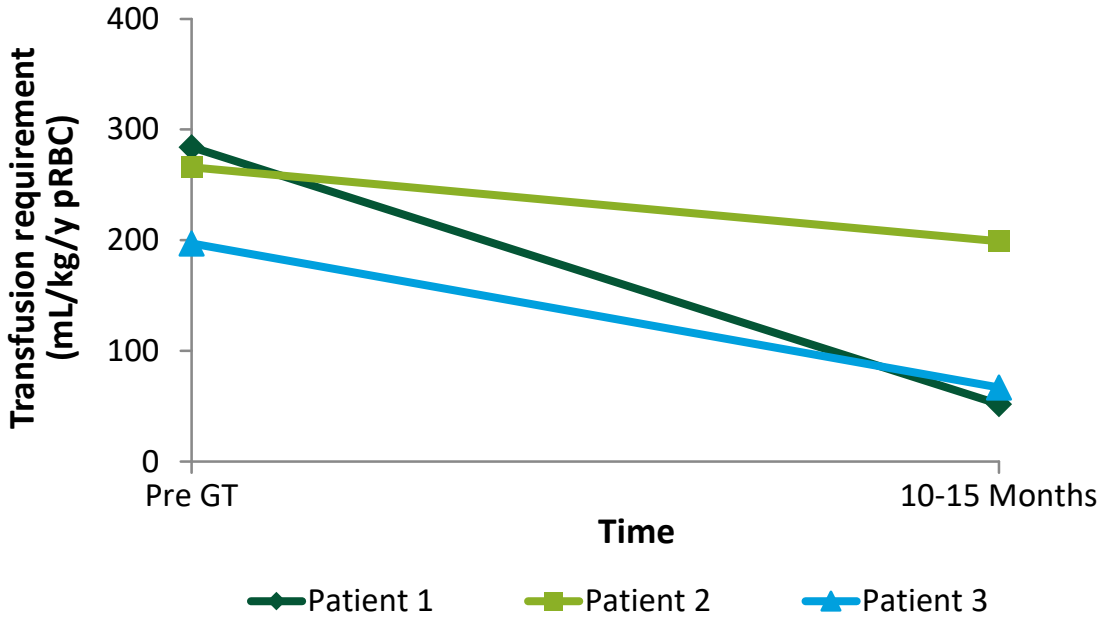
OTL-300 for TDT: Single Intervention with Evidence of Transfusion Independence

Proof-of-Concept data in 9 patients with more severe genotypes β0/β0, β+/β+ and β0/β+

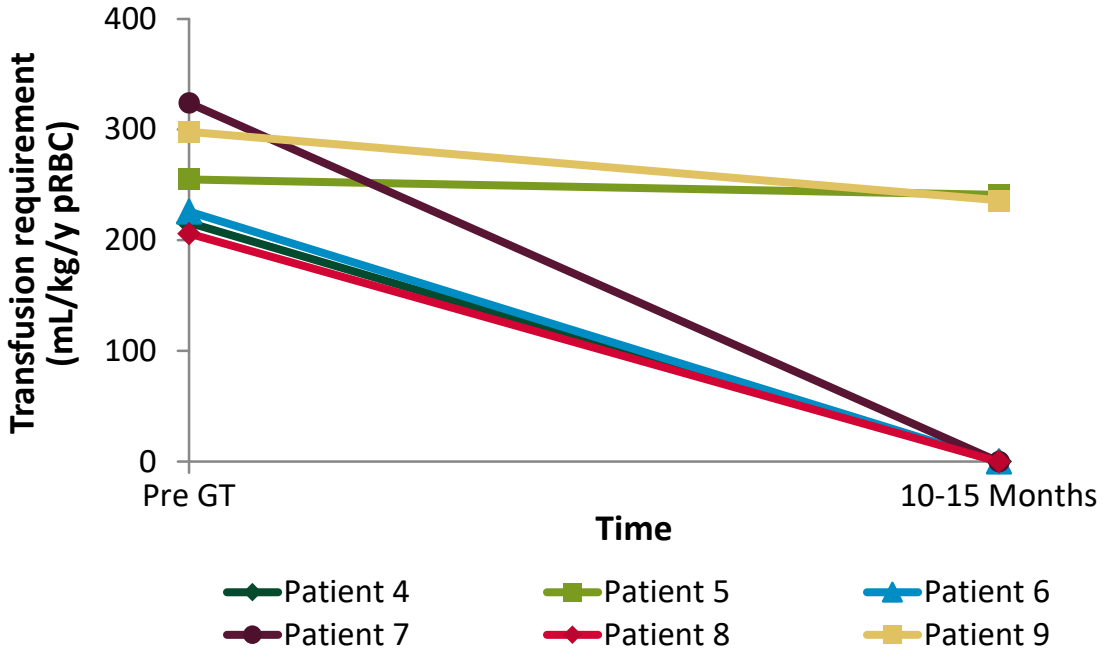
OTL-300 treatment outcomes

- Average transfusion requirement pre-gene therapy of ~250 (mL/kg/y pRBC)
- 8/9 patients with reduced or eliminated need for transfusions (5 pediatrics / 3 adults) at 12 months
- 4 pediatric patients transfusion-independent, including in β0/β0 and in severe β+ patients
- Adverse event profile consistent with autologous transplants, none related to the drug product

Adults (n=3)



Pediatrics (n=6)



Data presented at ASGCT 2019

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Manufacturing & Commercial Opportunity

CMO Infrastructure Established for First Three Planned Launches

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Orchard Therapeutics Supply Chain

Local Treatment of Patients in Hospital	Drug Product Manufacturing (Cell Processing)	Lentiviral Vector Manufacturing

Collect blood or bone marrow

Ship tissue to manufacturing facility

Isolate hematopoietic stem cells (HSCs)

Gene-modify HSCs with lentiviral vector

Cryopreserve HSC product

Ship cryopreserved product to hospital

Thaw and infuse product

Conditioning

Well Positioned to Supply Market Given Focus on Pediatric Diseases

Manufacture disease-specific lentiviral vector

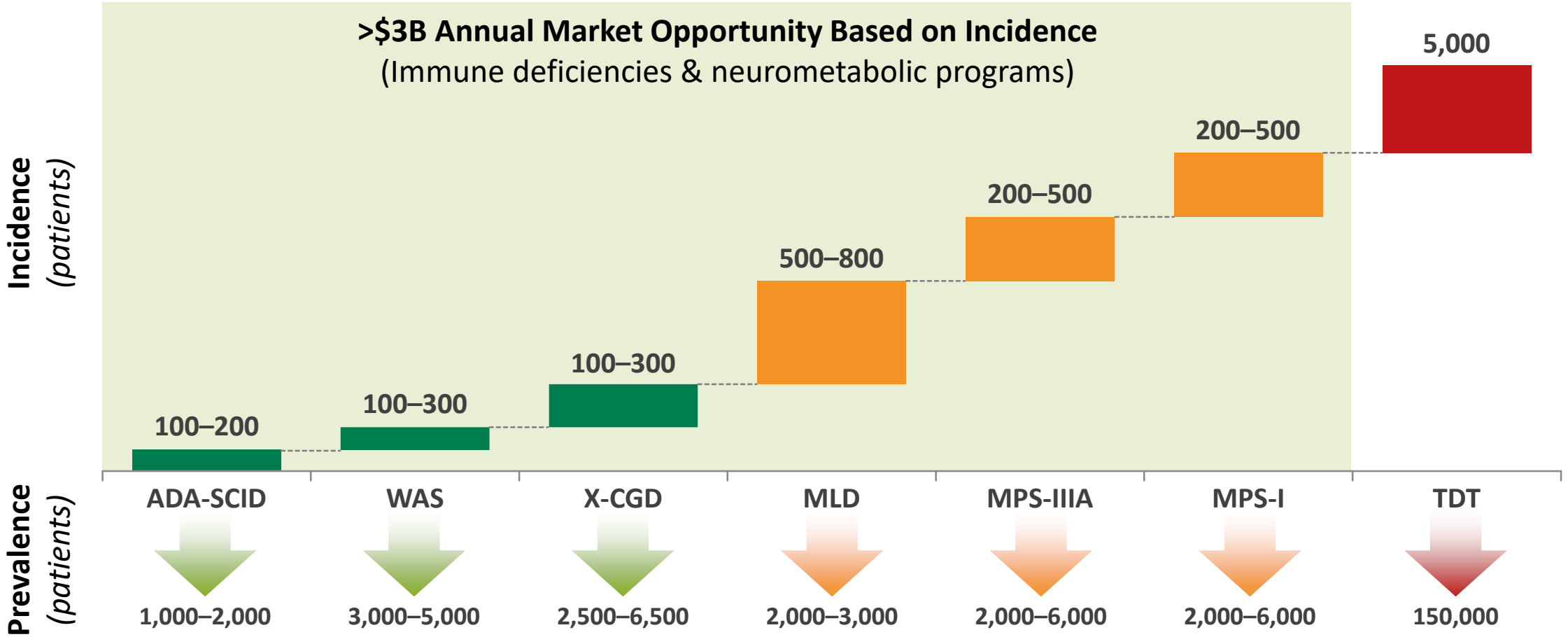
Lonza MOLMED

OxfordBioMedica MOLMED YPOSKESI

Investment in Orchard Manufacturing Facility to Provide Capacity and Long-term Security of Supply

Highly Scalable Business Model in Rare Disease

More than 6,000 new patients per year across clinical stage indications



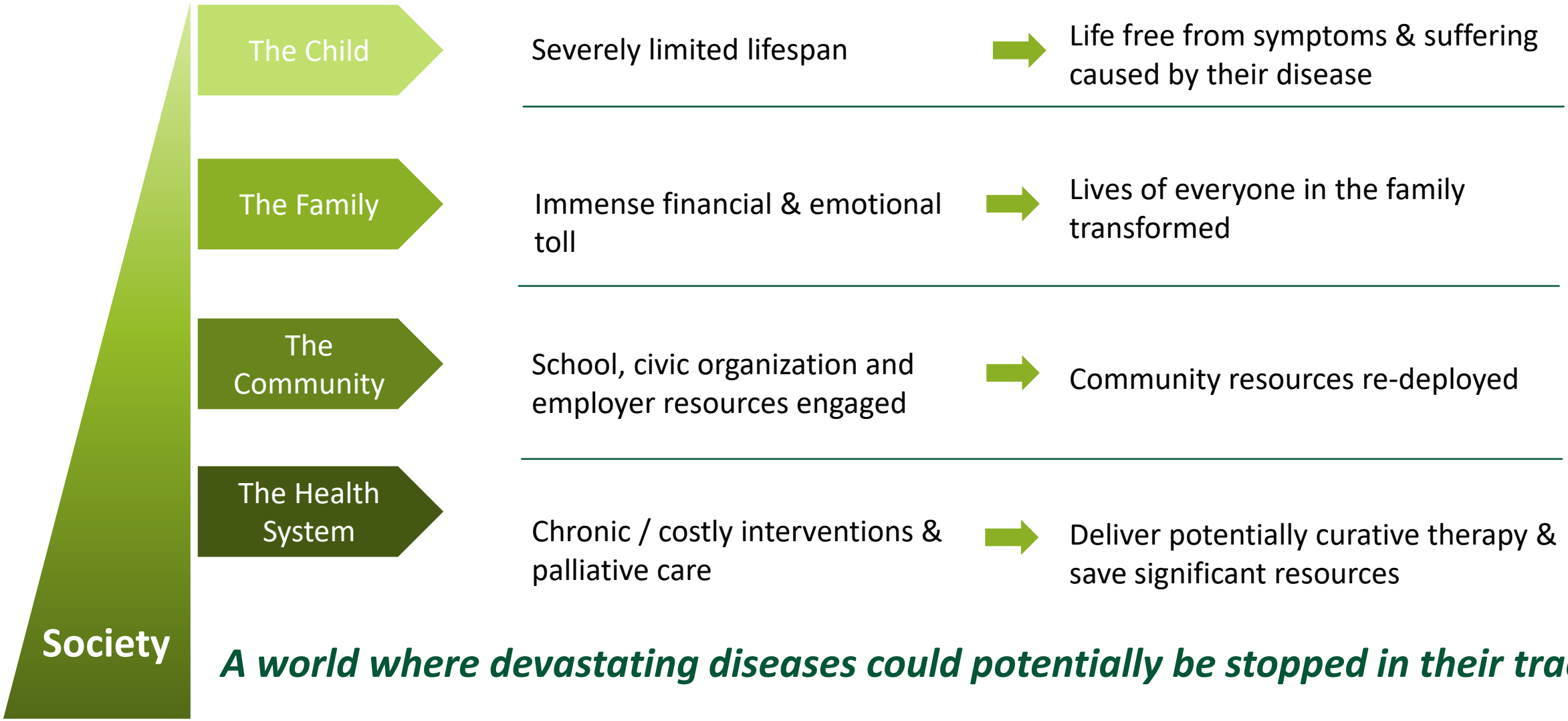
Significant revenue upside based on penetrating prevalent population in all diseases and TDT opportunity

Figures based on countries where rare disease therapies are typically reimbursed. Patient ID/diagnostics and access/reimbursement will further define addressable population.

Implementing Commercial Strategy to Launch Therapies Globally

1 Geographic Footprint	• Teams in place in EU & North America • Expanding to Latin America, Turkey, Middle East & Asia over time
2 Patient ID and Diagnostics	• Expand newborn screening (NBS) for ADA-SCID • Assay selection & NBS pilot testing for MLD • Disease awareness and advocacy
3 Centers of Excellence	• Select leading centers with transplant & disease area experience • Center qualification
4 Market Access	• Multi-stakeholder engagement • Gene therapy value determination for each program • Option for flexible payment models
5 Global Supply Network	• Manufacturing hub(s) to ship cryopreserved product globally

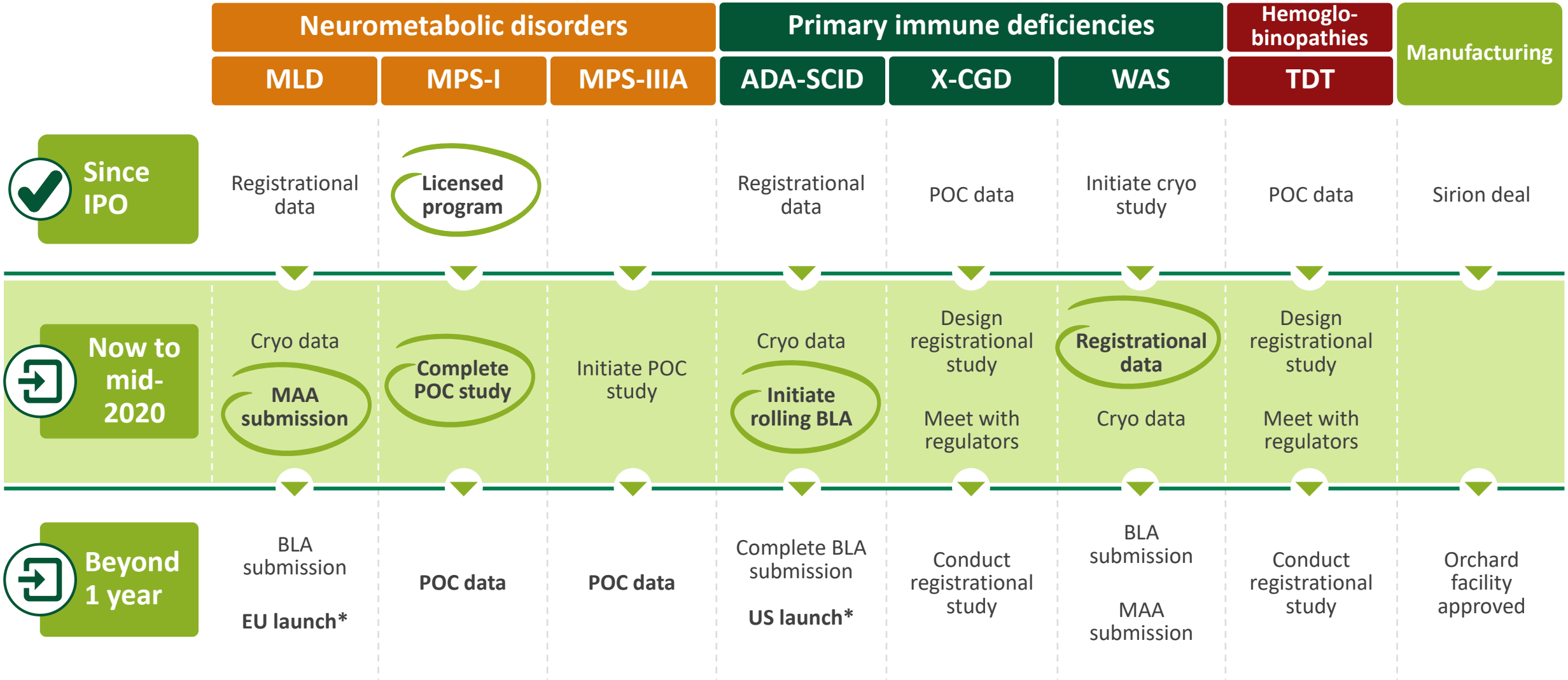
When We Think about Value, It All Starts with the Child
and What Our Therapies, If Approved, Could Do for That Child and Beyond



A world where devastating diseases could potentially be stopped in their tracks

Broad Pipeline Leads to Significant Near-term Clinical, Regulatory and Commercial Catalysts

Orchard therapeutics



US and EU launches assume granting of regulatory approvals

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