Orchard therapeutics

2018 Financial Results and Business Highlights

March 21, 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 Securities and Exchange Commission, including in the final prospectus related to the Company’s initial public offering filed with the Securities and Exchange Commission pursuant to Rule 424(b) of the Securities Act of 1933, as amended, as well as subsequent filings and reports filed with the Securities and Exchange Commission. 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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Mark Rothera
President & Chief Executive Officer

Agenda for Today's Call

1. Renee Leck, Director Investor Relations
   - Intro & Forward Looking Statements
2. Mark Rothera, President & Chief Executive Officer
   - Vision, Portfolio Overview and 2019 Priorities
3. Bobby Gaspar, M.D., Ph.D., Chief Scientific Officer
   - Platform & Primary Immune Deficiencies
4. Andrea Spezzi, MBBS, FFPM, Chief Medical Officer
   - Neurometabolic Disorders & Hemoglobinopathies
5. Frank Thomas, Chief Financial Officer
   - Financial Results & Upcoming Milestones

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







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

Global Leadership in Gene Therapy for Rare Diseases

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

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

Three submissions for product approvals anticipated over the next three years (MLD, ADA-SCID, WAS)

Recently announced X-CGD clinical POC (additional data at ASBMT); TDBT clinical POC expected in 2019

Establishing manufacturing capabilities to deliver products globally

Strong balance sheet entering 2019 with $340M in cash

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-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**
OTL-102	**X-CGD** (X-linked chronic granulomatous disease)				
Hemoglobinopathies					
OTL-300[3]	**TDBT** (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

Lead Indications Represent Potential >$2B Market Opportunity

Orchard Retains Full Commercial Rights to All Indications in All Markets

> $2B market opportunity based predominantly on incidence

prevalent population represents considerable upside

Data based on company estimates derived from published literature.

Numerous Data and Clinical Milestones Anticipated in 2019

3 Registrational Clinical Trial Data Sets

OTL-200 (MLD)
EBMT

2 & 3 year follow-up fresh formulation (n=20)
Cryo formulation engraftment data (n=3)

OTL-101 (ADA-SCID)
ASBMT

✓ 2 year follow-up fresh formulation (n=20)
Cryo formulation engraftment data (n=10)

OTL-103 (WAS)

3 year follow-up fresh formulation (n=8)

Clinical Trial Initiations & Other Milestones

OTL-103 (WAS)

Initiate cryo formulation trial

OTL-102 (X-CGD)

Design registrational trial & engage regulators

OTL-300 (TDBT)

Report data from POC trial (n=9)

OTL-201 (MPS-IIIA)

CTA submission & clinical trial initiation

CMO Infrastructure Established for First Three Launches

Recent CTO Appointment Strengthens Global Manufacturing & Supply Chain Leadership

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

Recently announced build-out of Orchard Freemont Manufacturing Facility to Provide Capacity and Long-term Security of Supply

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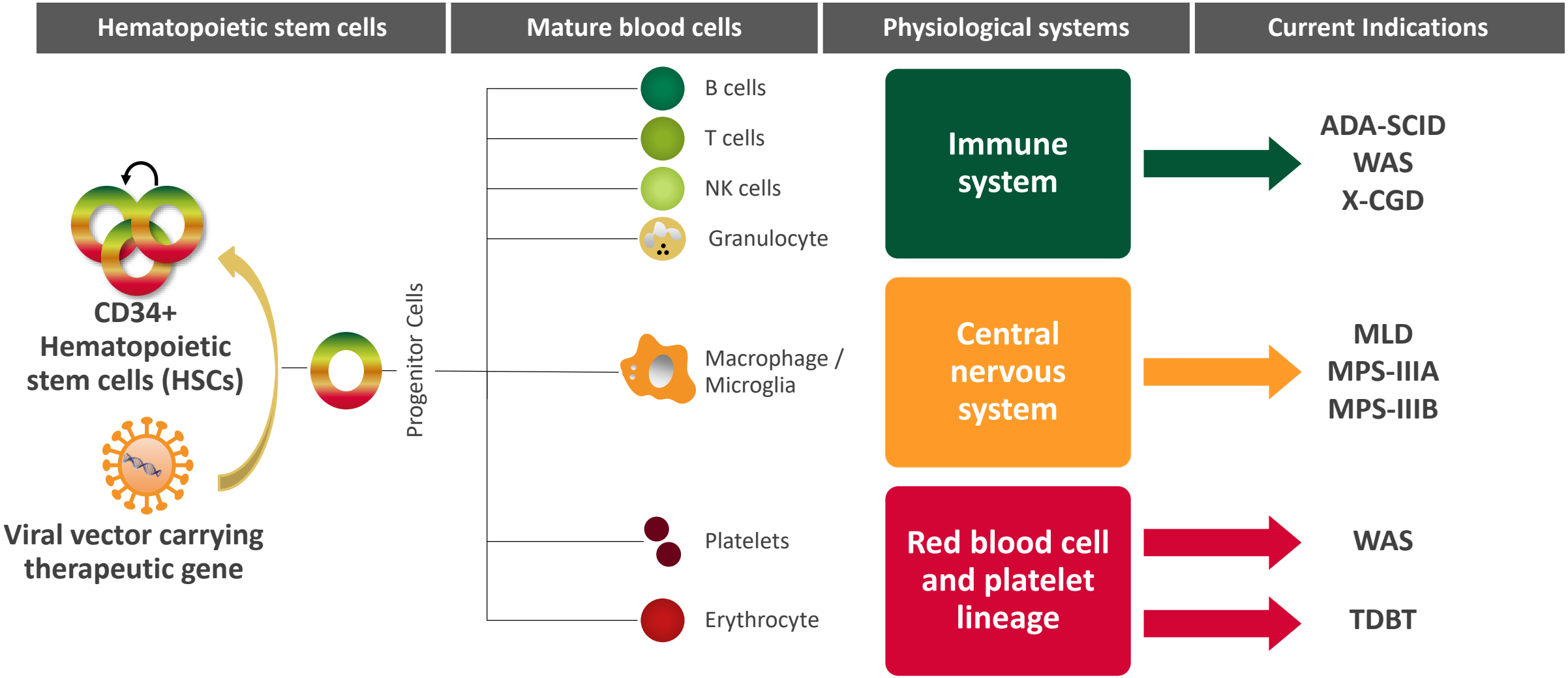
Bobby Gaspar, M.D., Ph.D.
Chief Scientific Officer

Delivering Therapeutic Genes to Multiple Physiological Systems



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

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)	32	8
Hemoglobinopathies	**OTL-300** (TDBT)	9	3

Persistent, Long-term Effects Across Five Indications with Over 150 Patients Treated

[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 as of December 2018
Data include all patients treated with CD34+ hematopoietic stem cells transduced *ex vivo* with vector of interest.

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

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1
Blood cell collection:
Blood hematopoietic stem cells (HSCs) and other progenitor cells are taken from the patient via leukapheresis or bone marrow extract

2
HSC selection & purification:
HSCs, identified by the CD34+ cell surface marker, are selected and purified by magnetic bead selection

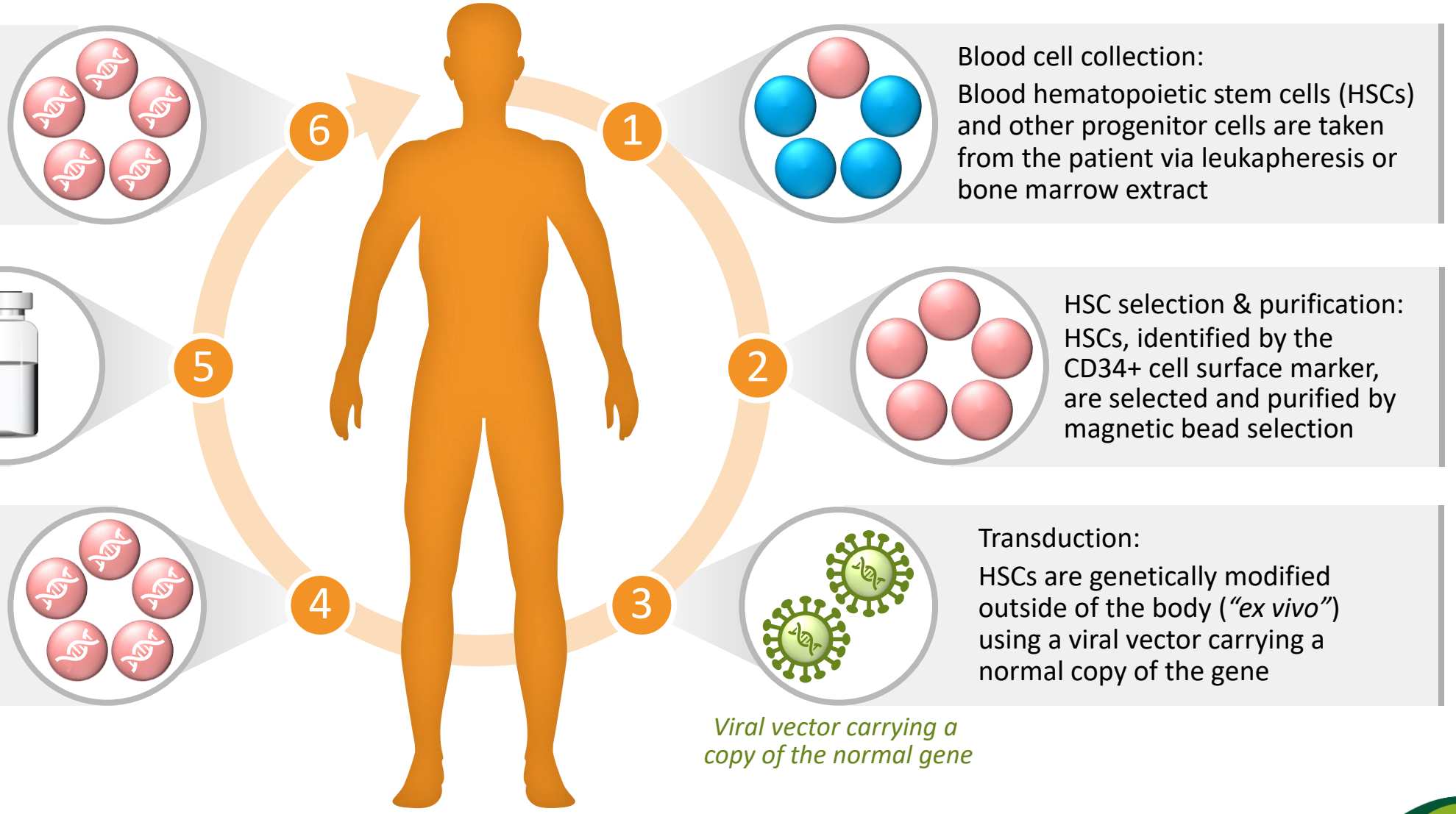
3
Transduction:
HSCs are genetically modified outside of the body (*"ex vivo"*) using a viral vector carrying a normal copy of the gene

Viral vector carrying a copy of the normal gene

4
Cryopreserved genetically modified HSCs

5
Conditioning:
The patient is given conditioning to "make space" for the genetically-modified cells

6
Administration:
Genetically-modified cells are given back to the patient



Life Threatening Inherited Immune Disorders: ADA-SCID, WAS and X-CGD

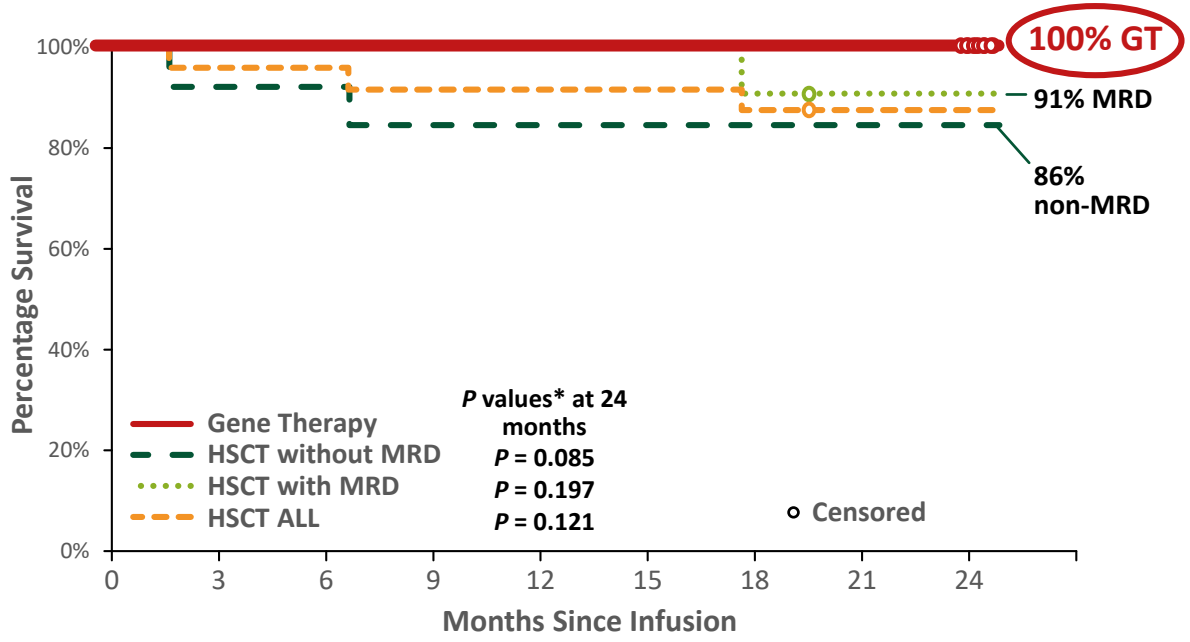
	Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID)	Wiskott-Aldrich Syndrome (WAS)	X-linked Chronic Granulomatous Disease (X-CGD)
Disease Overview / Symptoms	• Deficiency in ADA enzyme • T, B, and NK cell dysfunction • Recurrent and life-threatening severe infections • Incidence 80 – 180 patients per year	• Deficiency in WAS protein • Thrombocytopenia causing severe bleeding and infections, eczema, autoimmunity and life-threatening malignancies[1] • Incidence 100 – 260 patients per year	• Deficiency in NADPH oxidase function • Neutrophils / granulocytes unable to kill bacterial and fungal pathogens • Life-threatening, repeated chronic fungal and bacterial infections • Incidence 200 – 320 patients per year
Prognosis	• Usually fatal within first two years of life without treatment	• Median survival ~15 years with conservative treatment[2]	• ~40% mortality by age 35[3]
Current Treatment	• Strimvelis (EU only) • Allogenic HSCT • Chronic ERT	• Conservative care • Allogeneic HSCT	• Prophylactic antibiotics, antifungals and interferon • Allogeneic HSCT

[1] Oszahin (2008); Albert (2011); [2] Dupuis-Girod (2003); [3] van den Berg et. al, PLoS One. 2009;4(4):e5234.

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

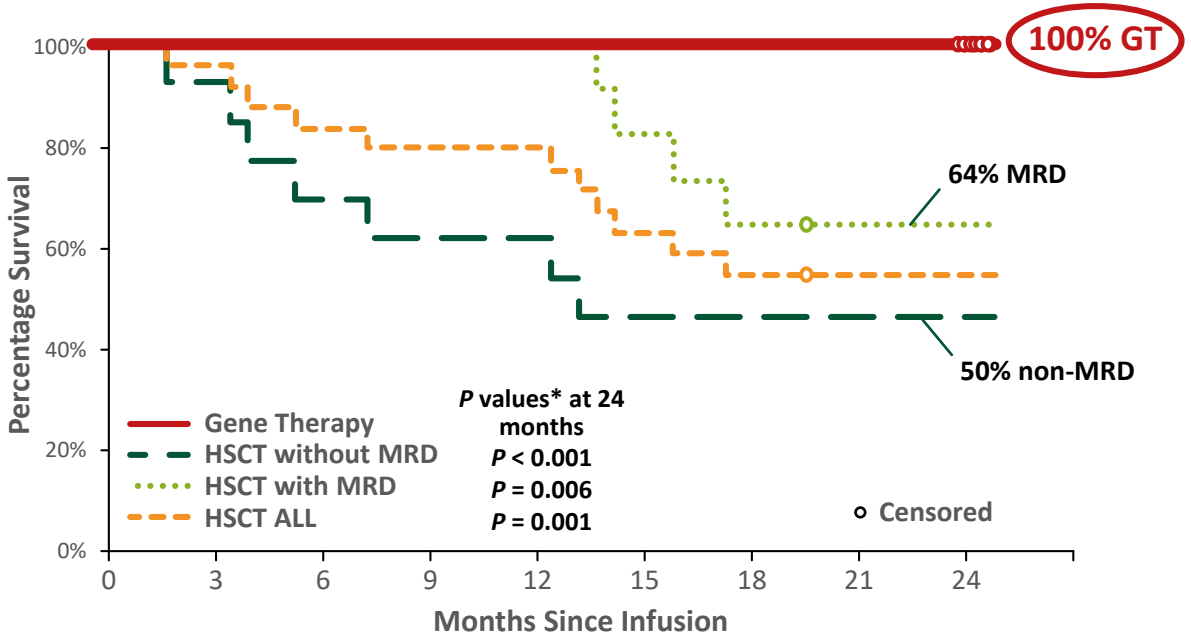
BLA Submission Expected in 2020 (followed by MAA)

Overall Survival



100% overall survival (n=20)

Event-free Survival



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

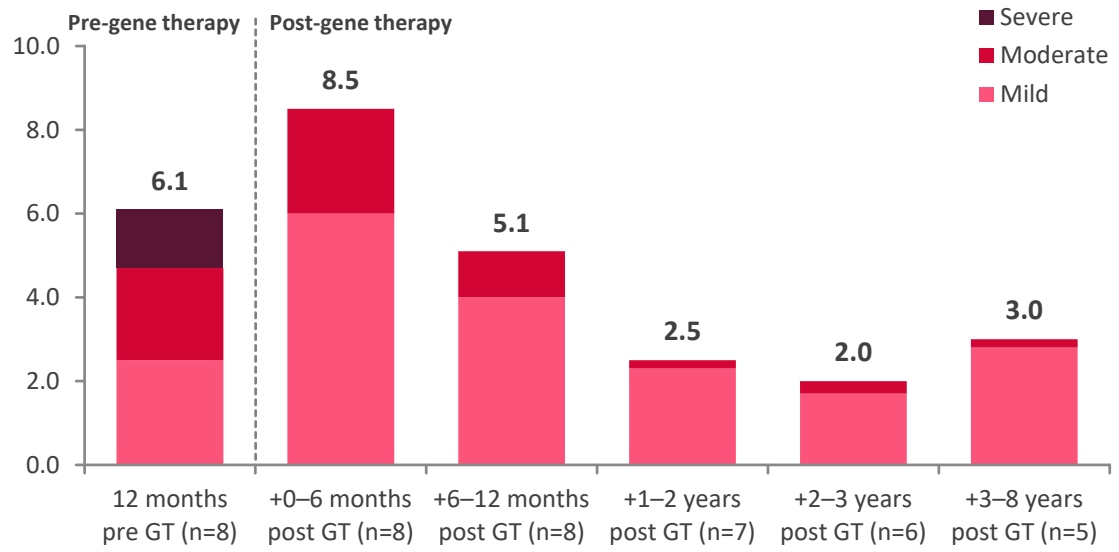
Data from registrational 2-year fresh cell product; n=20, presented at ASBMT 2019
*All P values are log-rank tests
One HSCT subject is excluded as they did not complete 24 months of follow-up

Event = survival without an event of reinstitution of PEG-ADA ERT or need for rescue HSCT

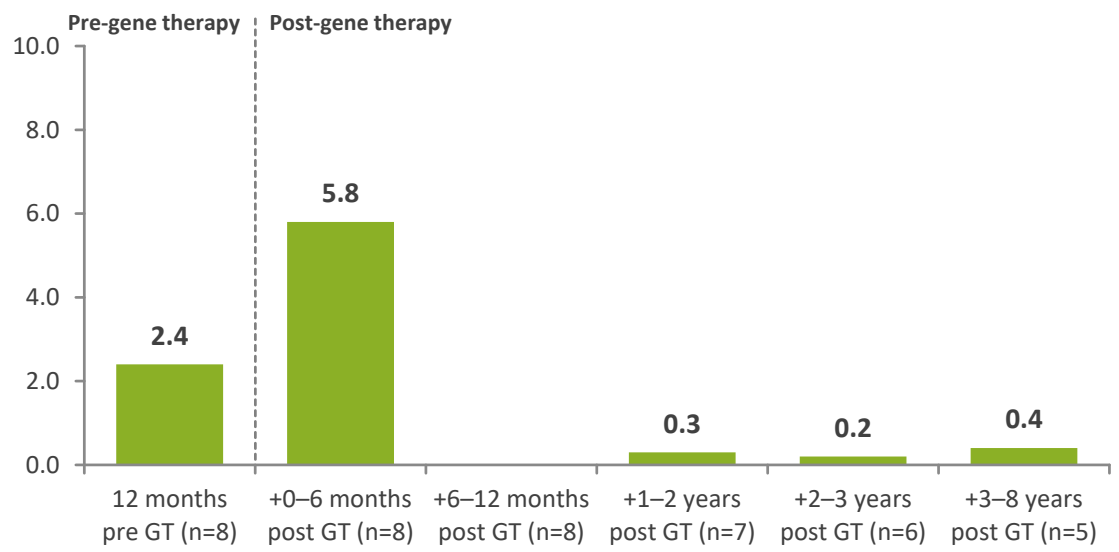
OTL-103 for WAS: Evidence of Consistent and Durable Efficacy

Cryo Trial to Initiate 2019; BLA/MAA Submission in 2021

Bleedings per patient per year



Severe infections per patient per year



Reduction in the rate of severe infections, bleeding events and hospitalizations

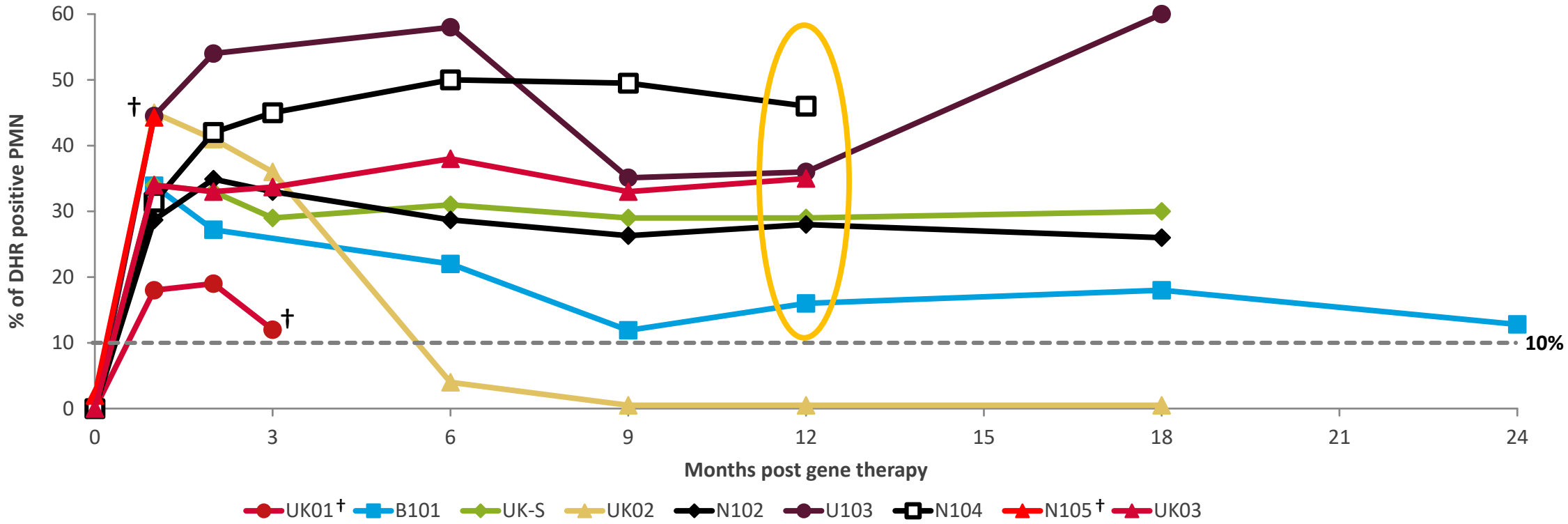
Well-tolerated among 16 patients treated (8 under clinical trials; 8 under compassionate use program)

Data based on interim clinical study report of 10 Jan 2017; 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 2019

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 as different from the OTL-102 drug product

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

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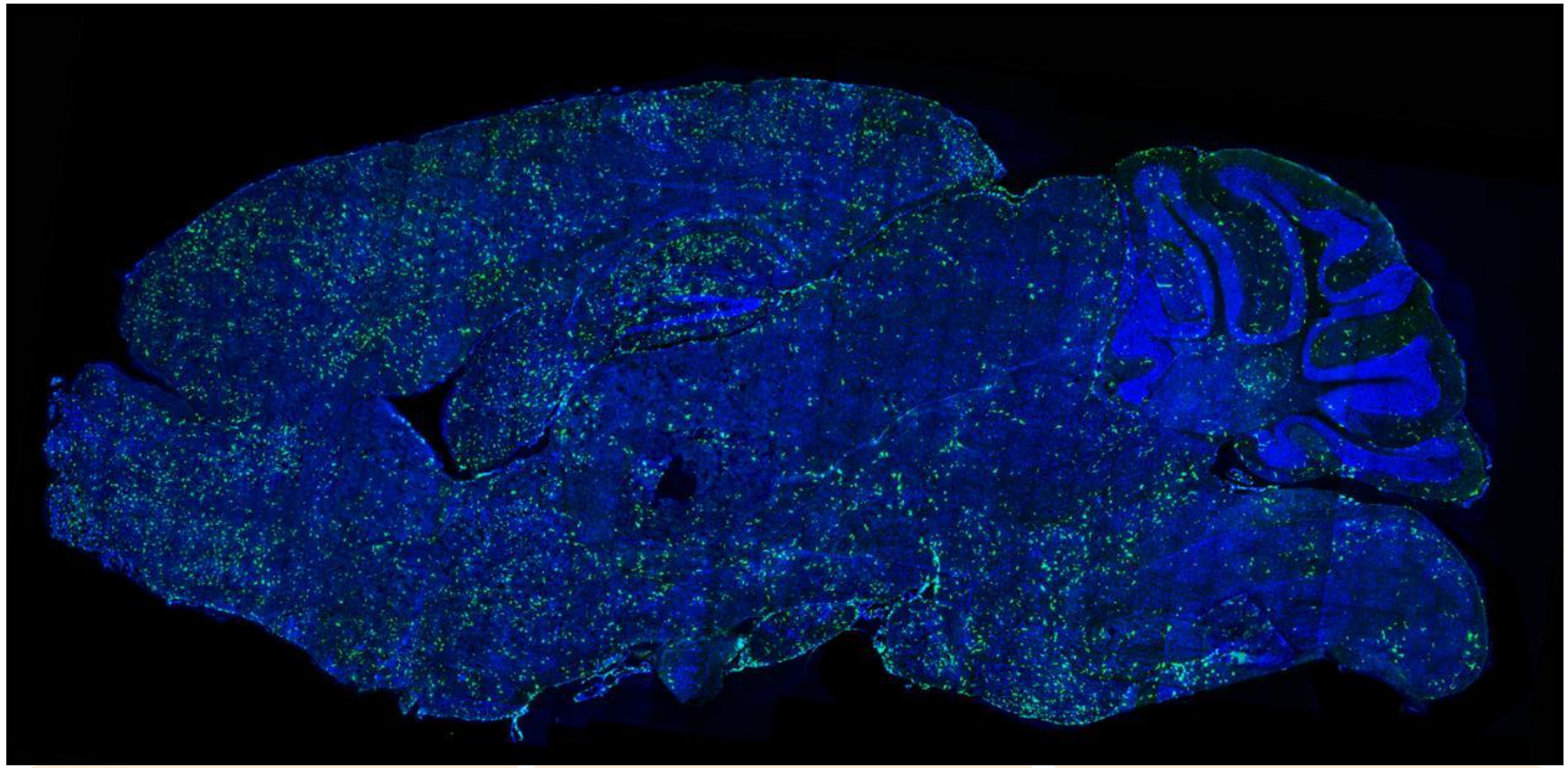
Broad transgene distribution in brain of mouse after administration of HSCs transduced with GFP-encoding vector



MLD | **MPS-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 HSPCs after Busulfan conditioning
Green = GFP (green fluorescent protein); **blue** = nuclei staining

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Andrea Spezzi, MBBS, FFPM
Chief Medical Officer

Devastating Neurometabolic Diseases with No Approved Treatment Options

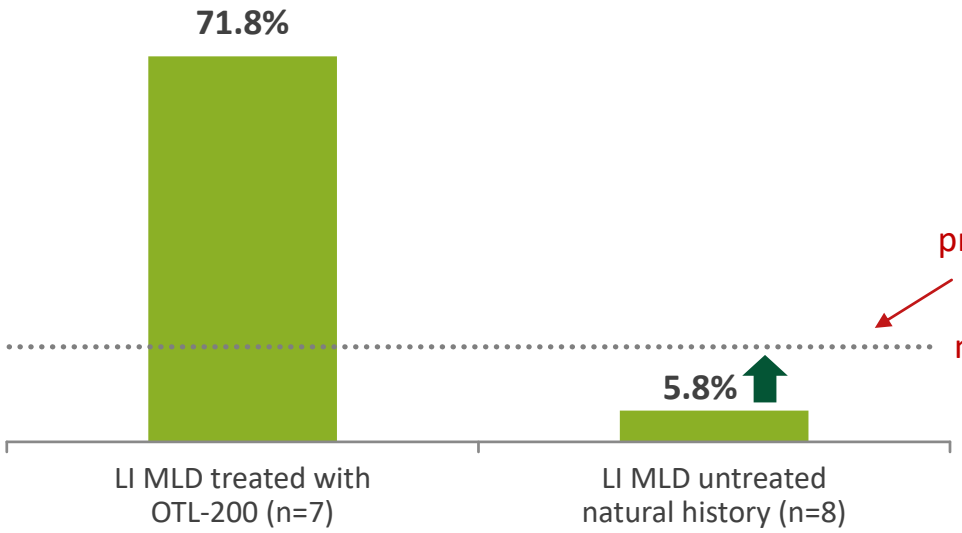
	Metachromatic Leukodystrophy (MLD)	Sanfilippo Syndrome Type A and Type B (MPS-IIIA, MPS-IIIB)
Disease Overview / Symptoms	• Deficiency in the ARSA[1] enzyme • Rapid & progressive neurodegeneration with loss of motor & cognitive function • Incidence: 400-770 patients per year	• Deficiencies in the SGSH (MPS-IIIA) and NAGLU (MPS-IIIB) enzymes • Progressive neurodegeneration, subsequent motor function decline; loss of language and mobility; seizures • MPS-IIIA incidence: 250-480 patients per year
Prognosis	• Severe form with high mortality rates: • Infantile: 50% at 5 years (onset 0-3 years)[2] • Juvenile: 44% at 10 years (onset 3-16 years)[2]	• Life expectancy: 10-25 years (MPA-IIIA) and 15-30 years (MPS-IIIB)
Current Treatment	• Largely palliative addressing symptoms • Very limited to no efficacy with allogeneic HSCT	• Largely palliative addressing symptoms • Allogeneic HSCT not shown to be effective[3] • ERT not effective treating neurological manifestations[4]

[1] ARSA: arylsulfatase-A; [2] Mahmood (2010); [3] Sergijenko (2013) and Boelens (2010); [4] Buhrman (2013)
SGSH: N-sulfoglycosamine sulfohydrolase; NAGLU: N-acetyl-alpha-glucosaminidase

OTL-200 for MLD: Significant Improvements in Motor Function

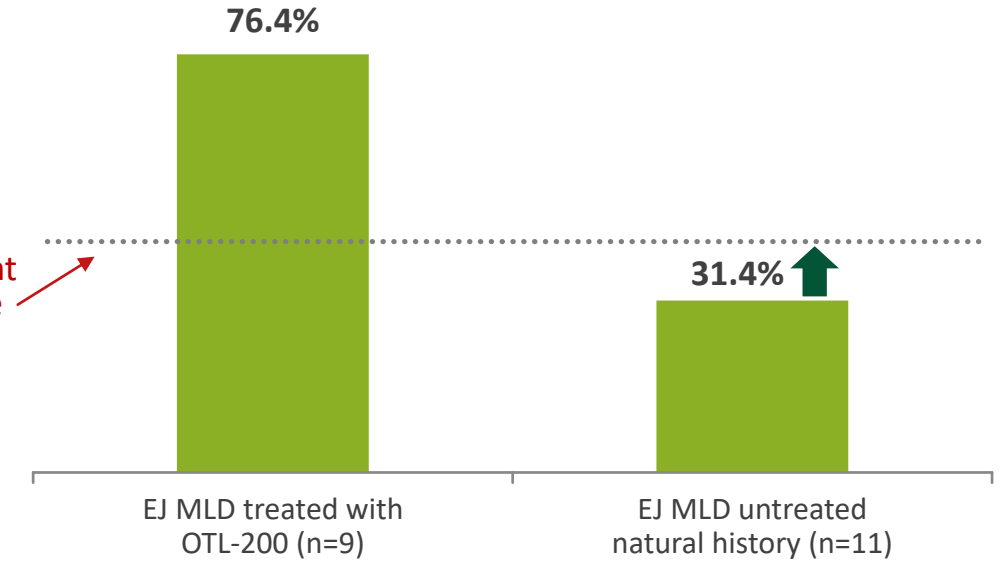
Three Year Data to be Presented at EBMT; MAA Submission Expected in 2020 (followed by BLA)

Late infantile MLD - GMFM Total Score
at 24 months post OTL-200 vs. natural history



66% treatment difference vs natural history

Early juvenile MLD - GMFM Total Score
at 24 months post OTL-200 vs. natural history



45% treatment difference vs natural history

Threshold for primary endpoint (10 percentage points above natural history)

32 patients treated (23 under clinical trials; 9 under compassionate use program)

Treatment difference (OTL-200 – untreated): 66.1% (LI) and 45% (EJ) respectively
Source: clinical study report (CSR) of 05 December 2017

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

CTA Submission for MPS-IIIA Expected in 2019

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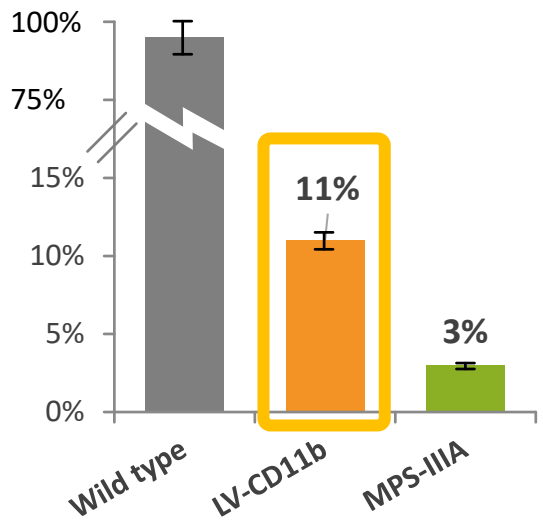
Increased enzyme expression in the brain

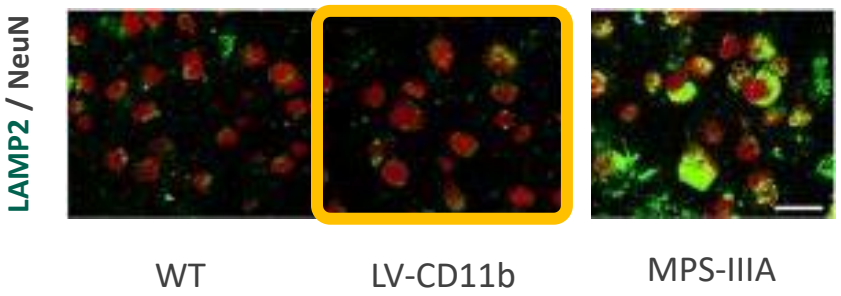
Percentage enzyme vs. wild type



11% enzyme expression vs. wild type

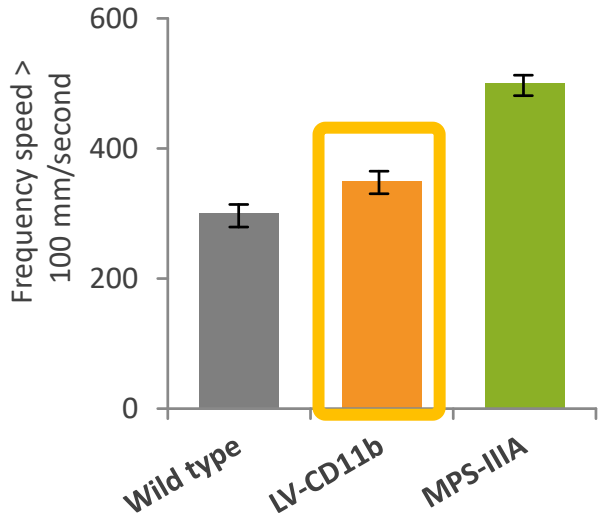
Decreased substrate accumulation in the brain

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

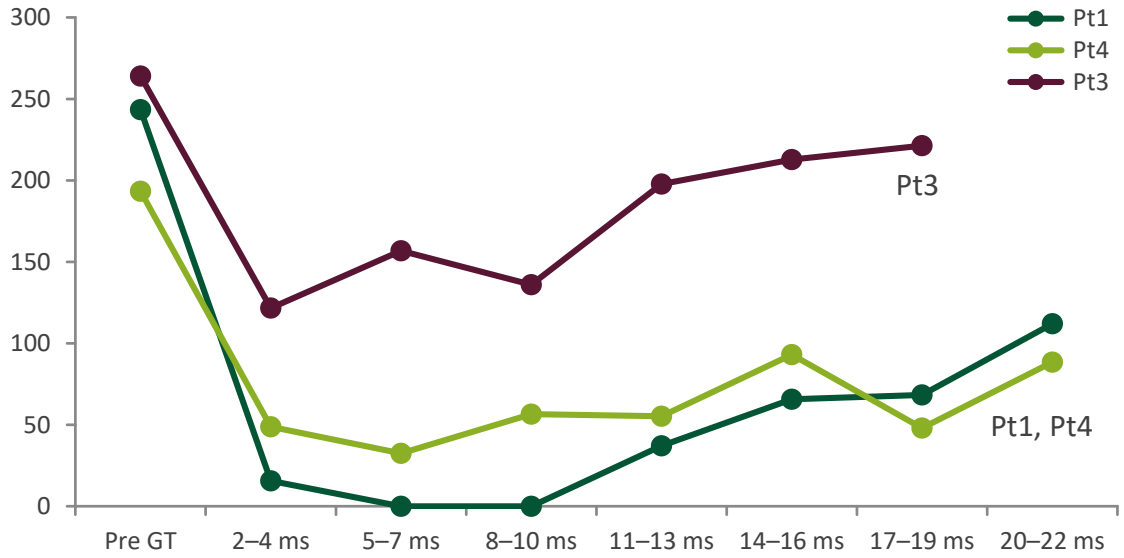
Transfusion-Dependent Beta-Thalassemia (TDBT): Inherited Blood Disorder with Significant Impact on Quality of Life

	Transfusion-Dependent Beta-Thalassemia (TDBT)
Disease Overview / Symptoms	• Deficiency in the hemoglobin-beta gene • TDBT (beta-thalassemia major) is the most severe form • Incidence: ~25,000 TDBT patients born each year, globally
Prognosis	• Usually fatal in infancy unless regular transfusions are initiated
Current Treatment	• Lifelong blood transfusions impacting quality of life and leading to long-term complications • Allogeneic transplants: risk of mortality and significant morbidity

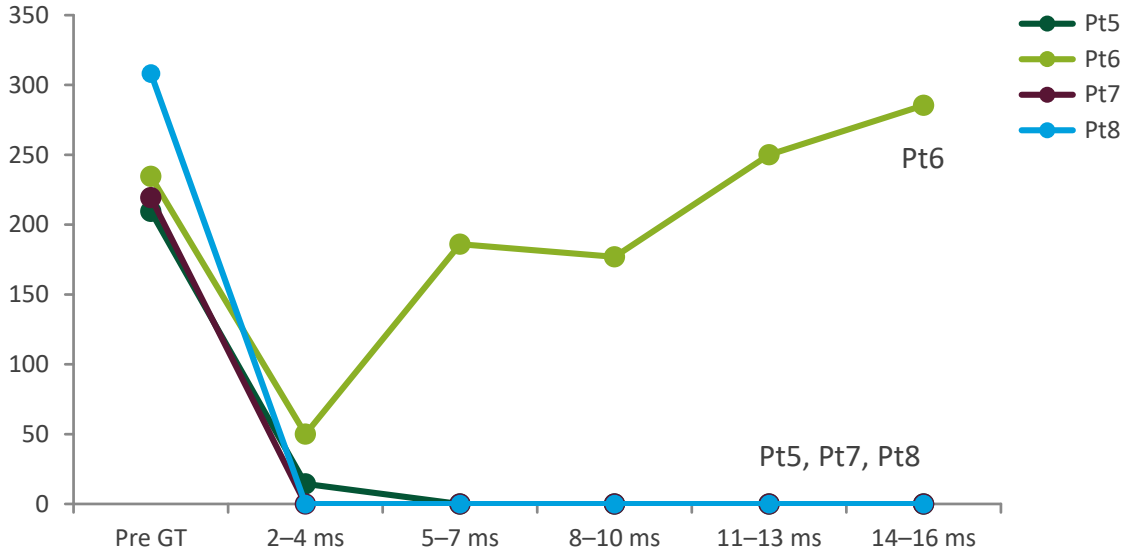
OTL-300 for TDBT: Single Intervention with Evidence of Transfusion-independence

Data in 7 Patients with More Severe Genotypes β0/β0, β+/β+, and β0/β+ Treated as of April 2018

Adult Patients (mL/Kg/y pRBC)



Pediatric Patients (mL/Kg/y pRBC)



OTL-300 treatment outcomes

- 5/7 patients with reduced need for transfusions (4 pediatrics / 3 adults)[1]
- 3/4 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

Data presented at the 2nd International Symposium on Red Blood Cells, Paris (17-20 April, 2018). Follow-up 4-31 months

[1] Transfusion data assessed for 7 out of 9 patients with sufficient follow-up (16-31 months); 2 patients with only 4 and 5 months follow-up, respectively

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Frank Thomas
Chief Financial Officer

Summary of 2018 Financial Results

Statement of Operations	Year Ended 12/31/18	Year Ended 12/31/17
Net product sales (Strimvelis®)	$2M	--
R&D Expenses	$205M	$33M
SG&A Expenses	$31M	$6M

Balance Sheet	Year Ended 12/31/18	Year Ended 12/31/17
Cash & investments	$340M	$90M

Cash and investments as of December 31, 2018 provide runway into second half of 2020

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3 year follow-up fresh formulation (n=8)

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Initiate cryo formulation trial

OTL-102 (X-CGD)

Design registrational trial & engage regulators

OTL-300 (TDBT)

Report data from POC trial (n=9)

OTL-201 (MPS-IIIA)

CTA submission & clinical trial initiation

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