Orchard therapeutics

Q1 Quarterly Investor Update

May 28, 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 Company’s annual report on Form 20-F filed with the Securities and Exchange Commission on March 22, 2019, 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.

Agenda for Today's Call

1. Renee Leck, Director Investor Relations
   - Intro & Forward Looking Statements
2. Mark Rothera, President & Chief Executive Officer
   - Vision, Today's Announcements & Q1 Highlights
3. Bobby Gaspar, M.D., Ph.D., Chief Scientific Officer
   - Updates in Neurometabolic Diseases
4. Frank Thomas, Chief Financial Officer and Chief Business Officer
   - New Credit Facility, Manufacturing, Q1 Financial Results
5. Mark Rothera, President & Chief Executive Officer
   - Commercial Opportunity / Market Access and Upcoming Milestones

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Mark Rothera
Vision, Today's Announcements & Q1 Highlights

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

Establishing manufacturing and distribution capabilities to deliver products globally

$300M in cash as of March 31, 2019, new $75 million credit facility extends runway into 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**
OTL-102	**X-CGD** (X-linked chronic granulomatous disease)				
Hemoglobinopathies					
OTL-300[3]	**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

Today's News: Expansion and Progress of the Neurometabolic Diseases Franchise

New collaboration for clinical program in MPS-I with preliminary data in four patients presented at ASGCT

Positive pre-MAA meeting for MLD and anticipated MAA submission brought forward to the first half of 2020

Clinical trial in MPS-IIIA now expected to start later this year with encouraging early results from 'specials' patient treated at Royal Manchester Children's Hospital

Numerous Data and Clinical Milestones 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)

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OTL-103 (WAS)

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Clinical Trial Initiations & Other Milestones

OTL-103 (WAS)

✓ Initiate cryo formulation trial

OTL-102 (X-CGD)

Design registrational trial & engage regulators

OTL-300 (TDT)

ASGCT

✓ Report data from POC trial (n=9)

OTL-201 (MPS-IIIA)

CTA submission & clinical trial initiation

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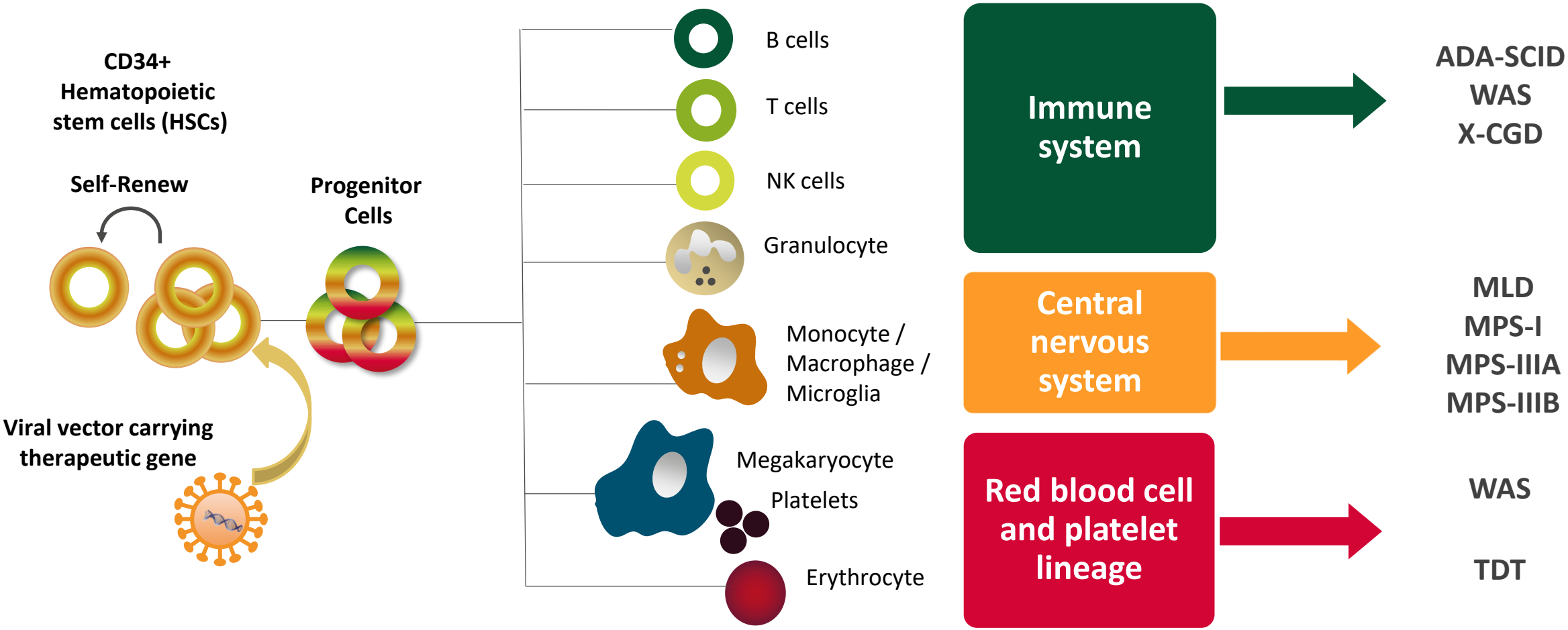
Bobby Gaspar, M.D., Ph.D., Chief Scientific Officer

Updates in Neurometabolic Diseases

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 Autologous *Ex Vivo* 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

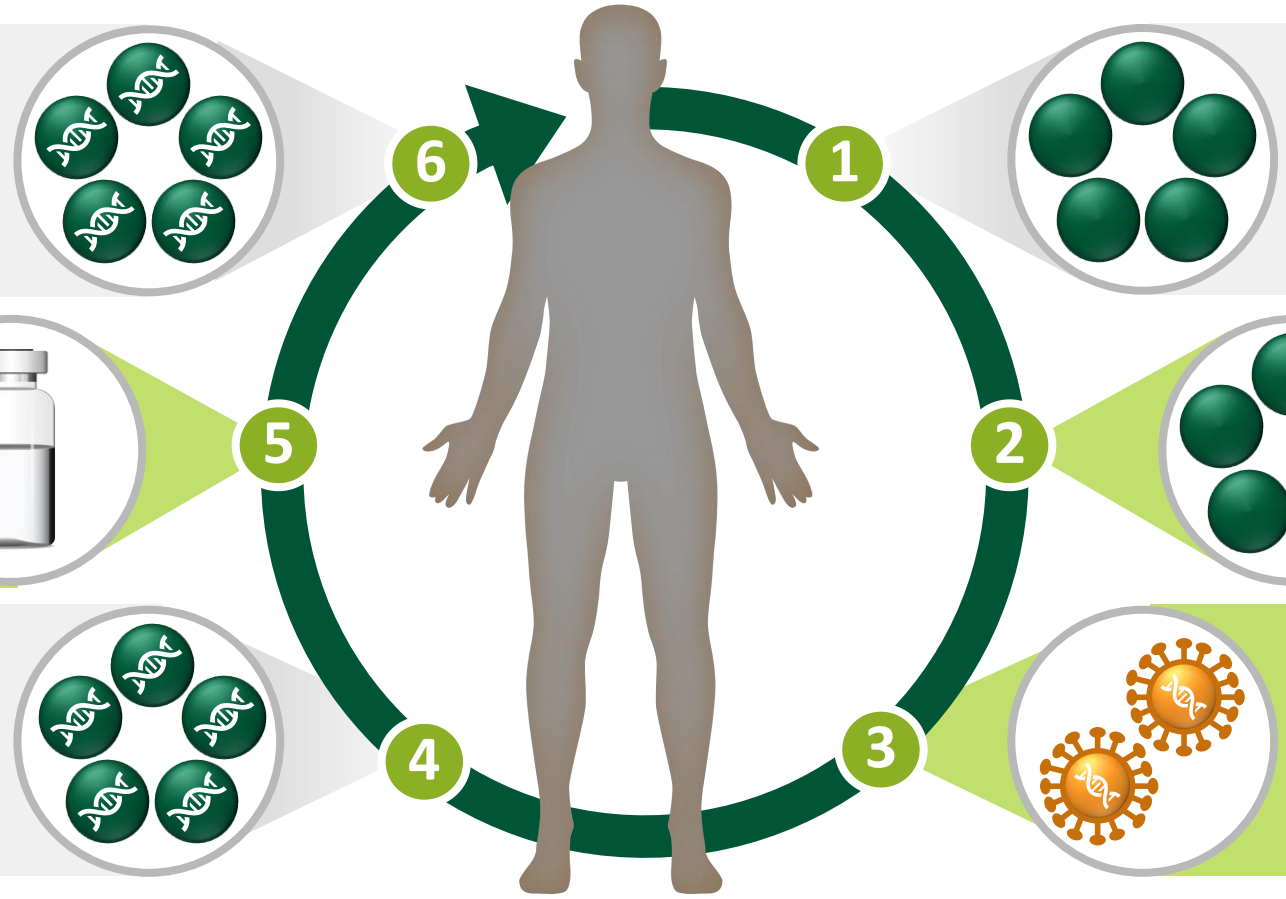
HSC selection and purification:
HSCs, identified by the CD34+ cell surface marker, are selected and purified by magnetic bead selection

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

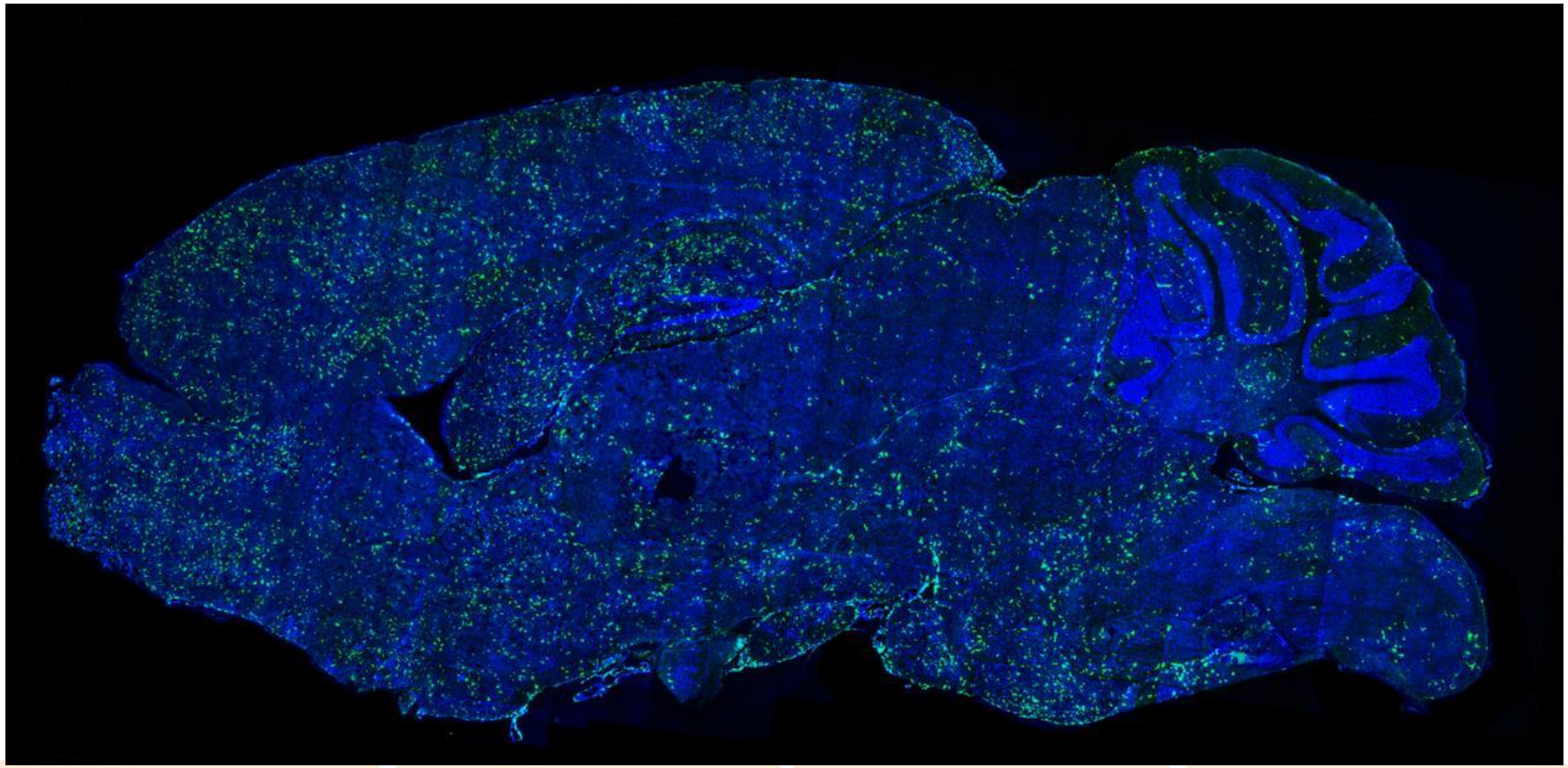


Viral vector carrying the functional gene

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.

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

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



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

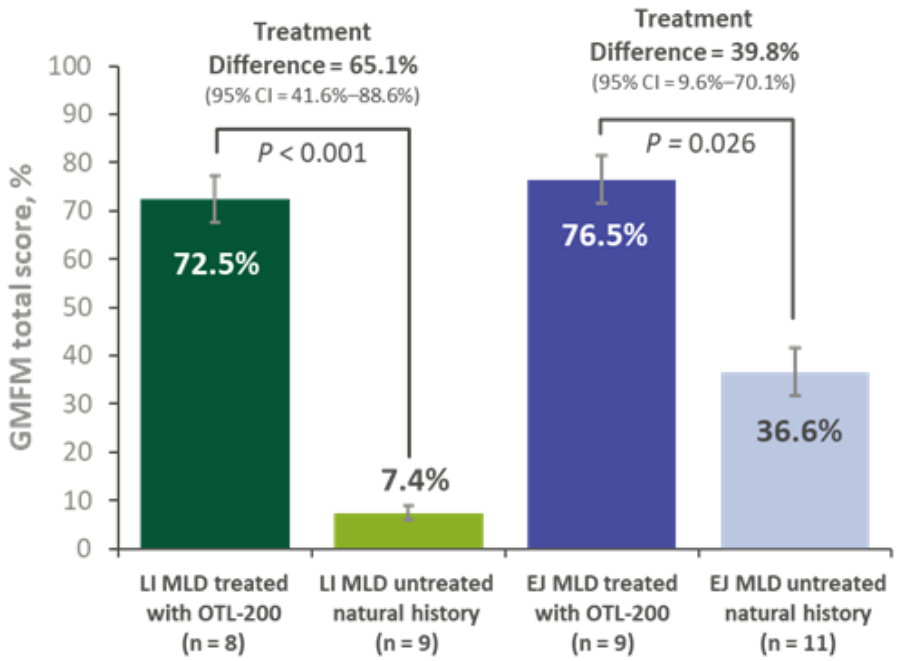
Multiple potential additional neurometabolic indications

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

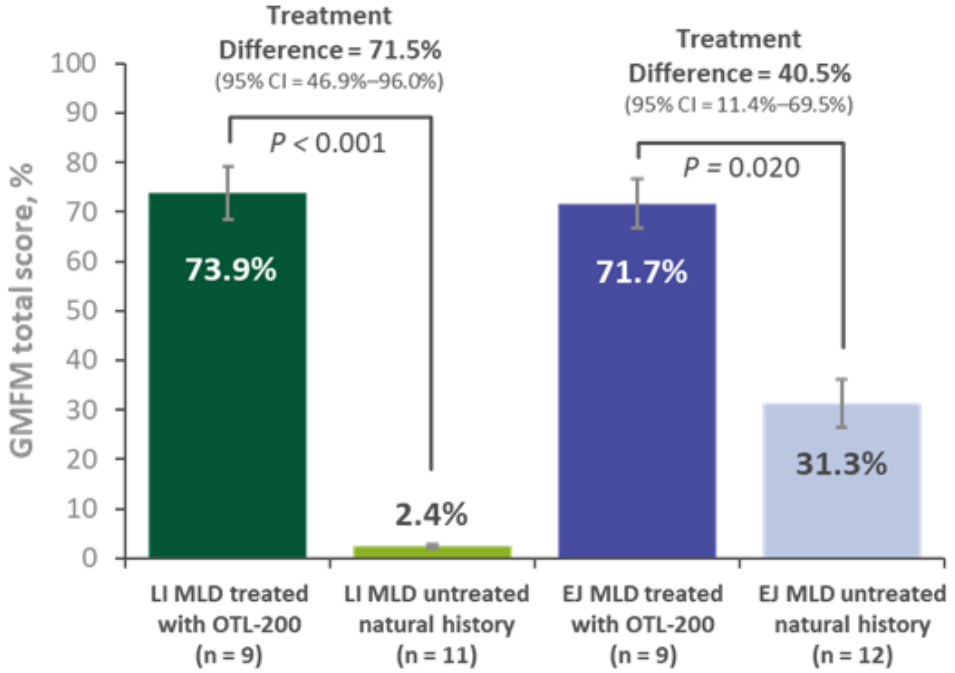
OTL-200 for MLD: Significant Improvements in Motor Function at Two and Three Years Post-Treatment Demonstrate Sustained Clinical Benefit

MAA submission brought forward to first half of 2020 (BLA submission approximately 1 year after)

2 Year (Co-primary Endpoint)



3 Year

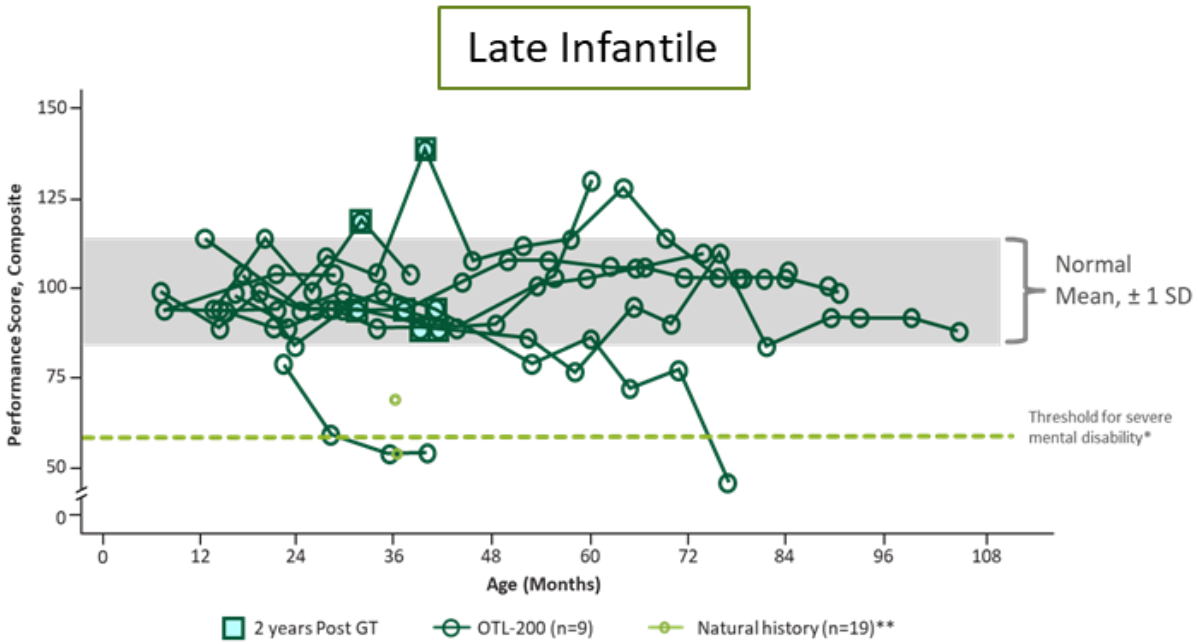


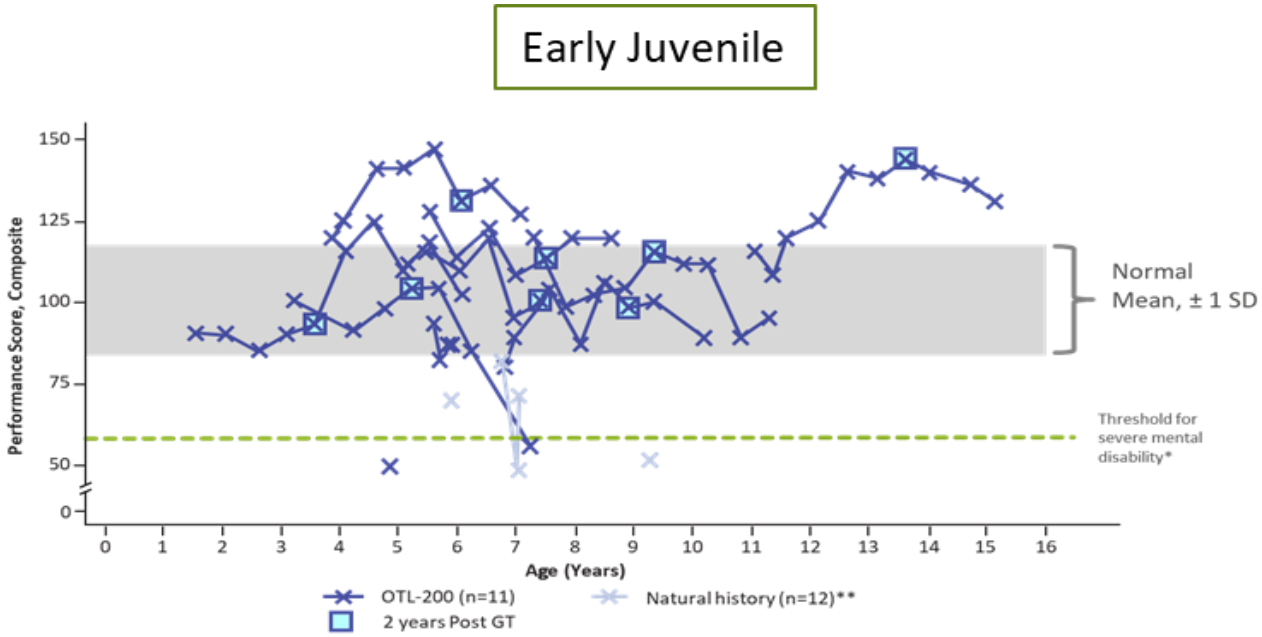
Up to 72% treatment difference in late infantile patients
40% treatment difference in early juvenile patients

Data presented 26 March 2019 at EBMT annual meeting

Vertical error bars are SE of the mean.; P-values are from a one-sided 2.5% hypothesis test with null hypothesis of a 10% difference
CI, confidence interval; EJ, early juvenile; GMFM, gross motor function measurement; GT, gene therapy; HSC, hematopoietic stem cell; LI, late infantile

OTL-200 for MLD: Cognitive Performance in Normal Range for Most Patients Post-Gene Therapy Independent of Their Symptomatic Status





Data presented 26 March 2019 at EBMT annual meeting

GT, gene therapy; MLD, metachromatic leukodystrophy. *Assessments below this line cannot be accurately measured and are subject to floor effects **Limited Natural history data is only available on cognitive scale appropriate for age

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: Proof of Concept Study Status

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

Study design

Study Design

- Key eligibility criteria:
  - Severe MPS-I clinical phenotype (Hurler)
  - Lack of allogeneic donor
  - Preserved neurocognitive function (DQ/IQ≥70)
  - With and without previous exposure to ERT
- Sample size: Up to 8 patients
- Intensive conditioning regimen
- Co-primary endpoints
  - Safety
  - IDUA enzyme activity in dried blood spots (up to supraphysiological levels) at 1 year post-treatment

Findings to date

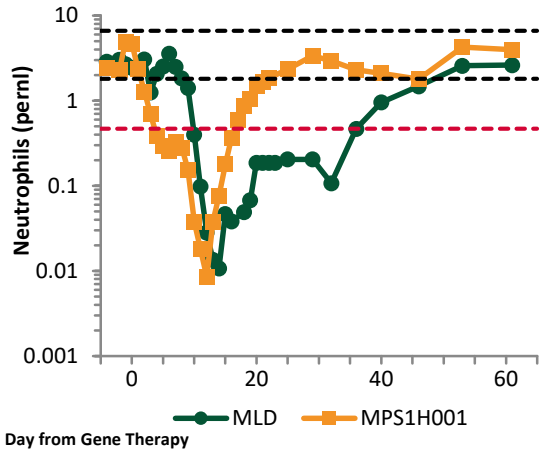
4 patients treated as of ASGCT, 3 with available data, follow-up out to 9 months in 1 patient

- Fast hematological reconstitution
- High level of transduction efficiency and engraftment
- Supraphysiological expression of IDUA enzyme in blood and cerebrospinal fluid (CSF)
- Normalization of urinary glycosaminoglycans (GAGs)
- Well-tolerated conditioning regimen

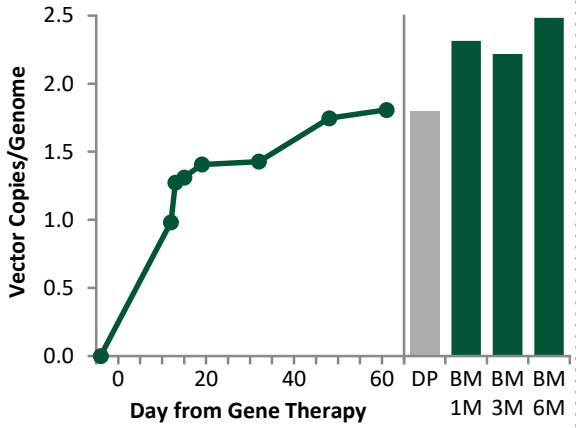
Data presented 29 April 2019 at ASGCT annual meeting

OTL-203 for MPS-I: Encouraging Preliminary Clinical Data in Patient with Nine Months of Follow-up

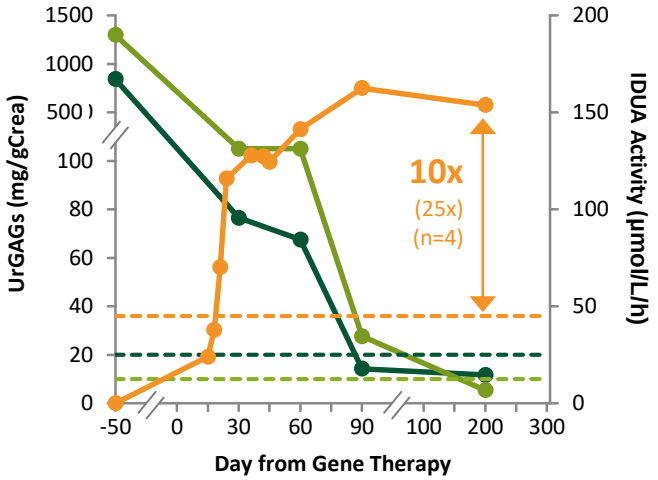
Rapid hematological reconstitution



Engraftment – significant VCN achieved within 60 days



Peripheral PD effects – Enzyme activity in dried blood spots and GAGs



- Supraphysiological IDUA enzyme activity (yellow line)
- Normalization of glycosaminoglycans (GAGs) at 6 months (green lines)

Central PD effects – Enzyme activity in CSF

- Supraphysiological expression of IDUA enzyme in CSF (~3x over normal range at 6 months)
- Significant reduction in CSF GAGs

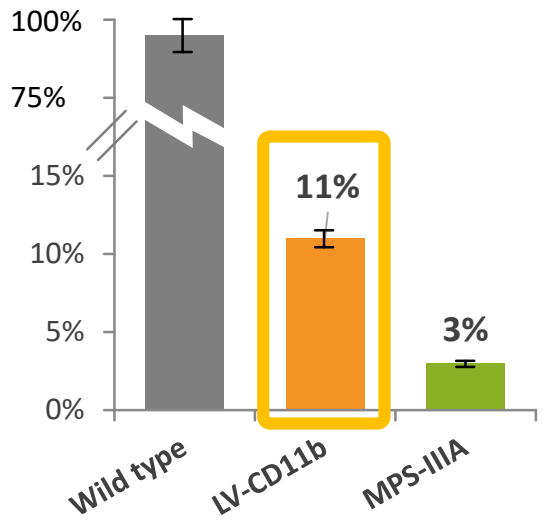
Data presented 29 April 2019 at American Society of Gene and Cell Therapy annual meeting; PD (pharmacodynamic); VCN (vector copy number)

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

Increased enzyme expression in the brain

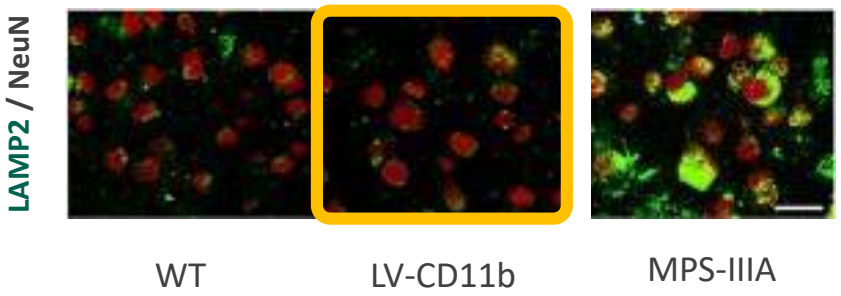
Percentage enzyme vs. wild type



11% enzyme expression vs. wild type

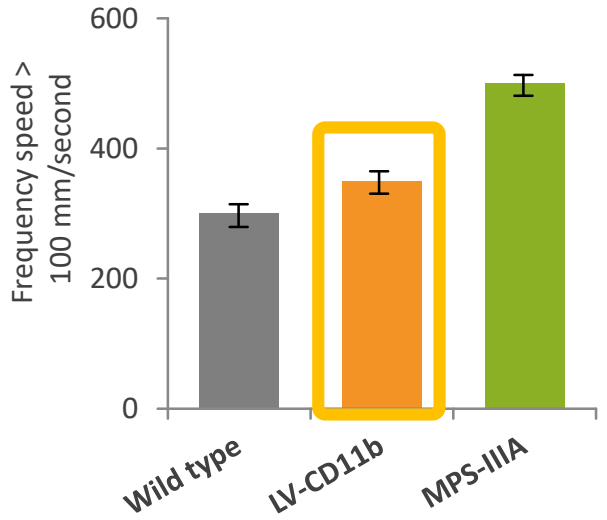
Decreased substrate accumulation in the brain

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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Frank Thomas
Manufacturing & Q1 Financials

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

Recent Highlights & Summary of First Quarter 2019 Financial Results

- Newly secured $75 million credit facility extends runway into 2021
  - 5 year senior credit facility with MidCap Financial
  - Supports investment of Orchard manufacturing facility
- MPS-I deal highlights business development strategy
- Innovations in manufacturing via transduction enhancers, stable cell lines and automated cell processing

Statement of Operations	Quarter Ended 3/31/19	Quarter Ended 3/31/18
R&D Expenses	$17.5M	$9.2M
SG&A Expenses	$10.8M	$4.5M

Balance Sheet	Quarter Ended 3/31/19	Year Ended 12/31/18
Cash & investments	~$300M	$340M

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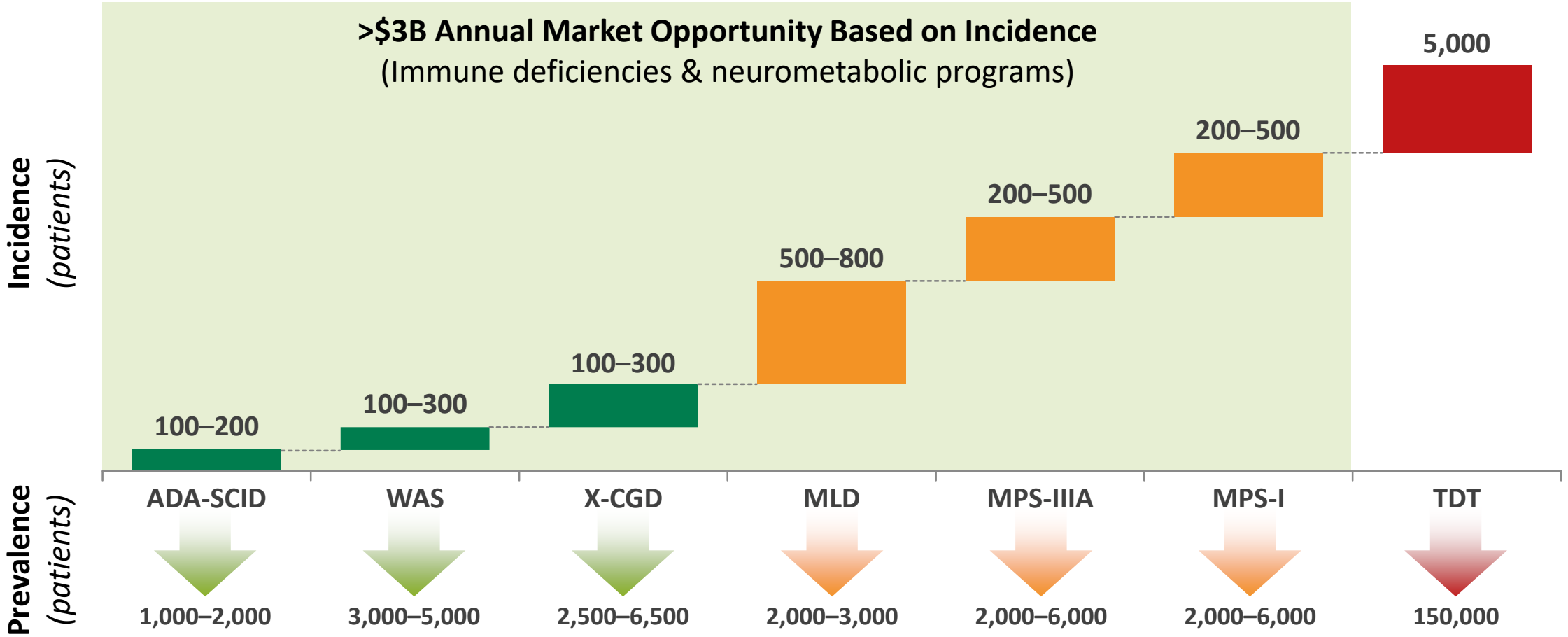
Mark Rothera
Commercial Opportunity / Market Access and Upcoming Milestones

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 populations 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.

Market Access for High-Value Single Administration Medicines

Tenets of our approach

NEAR-TERM:

Offer range of options to meet varying payer preferences within current system

LONG-TERM:

Collaborate to evolve payment system & overcome current barriers to novel payment approaches

MITNEWDIGS
NEW Drug Development ParadIGmS Initiative

> Precision Financing tools to enhance patient access to durable therapies must be tailored to the preferences, processes and constraints of each payer segment.

MIT NEWDIGS FoCUS Project

Massachusetts Institute of Technology

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Design registrational trial & engage regulators

OTL-300 (TDT)

ASGCT

✓ Report data from POC trial (n=9)

OTL-201 (MPS-IIIA)

CTA submission & clinical trial initiation

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

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	Neurometabolic disorders			Primary immune deficiencies			Hemoglo-binopathies	Manufacturing
	MLD	MPS-I	MPS-IIIA	ADA-SCID	X-CGD	WAS	TDT	
Since IPO	Registrational data	**Licensed program**		Registrational data	POC data	Initiate cryo study	POC data	Sirion deal
Next 12 months	Cryo data **MAA submission**	**Complete POC study**	Initiate POC study	Cryo data **Initiate rolling BLA**	Design registrational study Meet with regulators	**Registrational data** Cryo data	Design registrational study Meet with regulators	
Beyond 1 year	BLA submission **EU launch***	**POC data**	**POC data**	Complete BLA submission **US launch***	Conduct registrational study	BLA submission MAA submission	Conduct registrational study	Orchard facility approved

US and EU launches assume granting of regulatory approvals

Orchard therapeutics

Transforming the lives of patients through innovative gene therapies

www.orchard-tx.com