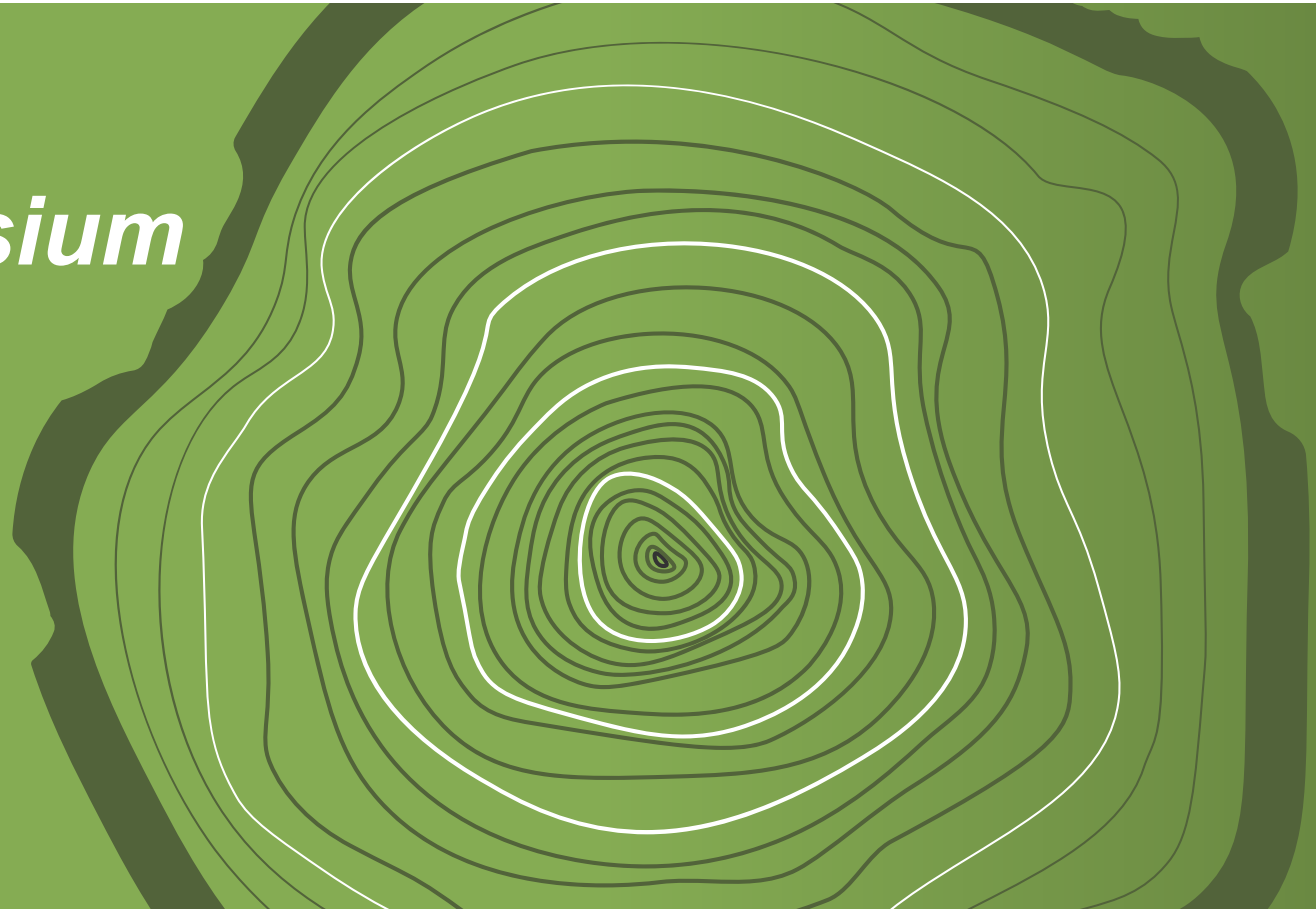
Orchard therapeutics™

2021 WORLD*Symposium*



Investor Webcast

February 9, 2021

Today's Agenda

TOPIC	SPEAKER
Introduction	Renee Leck
Compelling Data in Neurodegenerative Disorders with HSC Gene Therapy	Bobby Gaspar
MPS-IH Treatment Landscape Overview	Simon Jones
OTL-203 for MPS-IH Clinical Data	Bobby Gaspar
OTL-201 for MPS-IIIA Initial Data	Simon Jones
Q&A Session	

Forward Looking Statements and Disclosures

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 filed with the SEC on November 3, 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.

Dr. Simon Jones is a member of Orchard's Scientific Advisory Board and serves as a consultant to Orchard.

Orchard therapeutics

Compelling Data in Neurodegenerative Disorders with HSC Gene Therapy

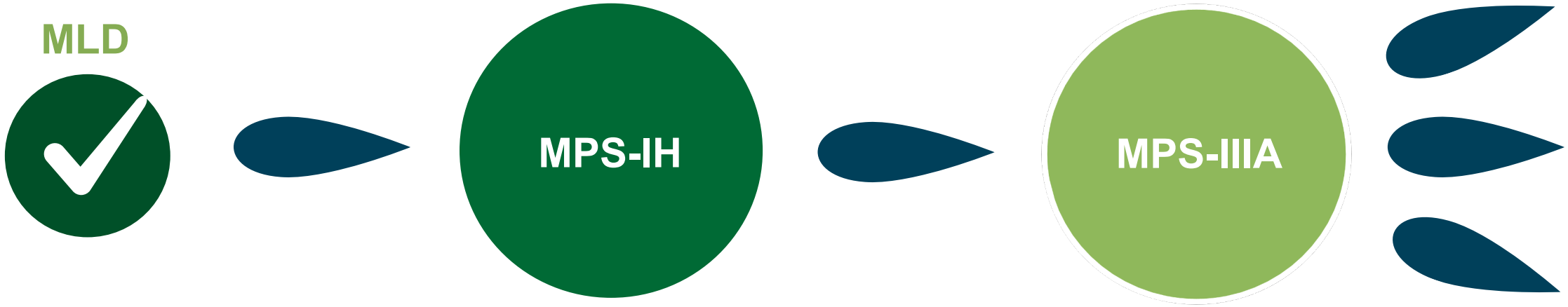
Dr. Bobby Gaspar

CEO of Orchard Therapeutics

Orchard therapeutics™

Growing Body of Patient Data in Neurodegenerative Disorders

Expected Program Milestones



- Libmeldy™ European launch (1H 2021)
- OTL-200 U.S. IND open + RMAT received

- OTL-203 parallel scientific advice with regulators (ongoing)
- Initiate OTL-203 registrational study (YE 2021)

- OTL-201 4th patient enrolled in POC study
- Complete enrollment and present interim data from OTL-201 POC study (2021)

Orchard therapeutics™

New Clinical Data from Neurodegenerative Programs at WORLD*Symposium*™

Nine Orchard Abstracts Accepted Showcasing Strength of HSC Approach

OTL-203 for MPS-IH

Emerging clinical profile

All eight patients show early clinical benefits across a range of outcomes, including cognition and growth

OTL-201 for MPS-IIIA

Promising initial biomarker data

Hematological engraftment and supraphysiological SGSH enzyme activity (all patients)

Substrate reduction to normal levels (first 2 patients)

MPS-IH Treatment Landscape Overview

Dr. Simon Jones

Manchester Centre for Genomic Medicine

Orchard therapeutics™

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

Disease

- Deficiency of IDUA enzyme leads to accumulation of heparan and dermatan sulfate
- Severe cognitive defects, growth abnormalities and extensive somatic pathologies (skeletal dysplasia, cardiomyopathy, loss of vision and hearing)

Epidemiology & Newborn screening

- Incidence: ~1 in 100,000 live births (all MPS-I); Hurler syndrome accounts for 60%[1]
- Prevalence: Potential to treat non-Hurler patients and/or patients on ERT over time
- NBS early adopters:[2]
  - EMEA: Italy*, Netherlands
  - U.S.: Added to the RUSP in 2015; with 23 states screening as of January 2021
  - Other: Canada, Taiwan
- NBS pilots and studies underway:[2]
  - Brazil, Mexico, Japan, Australia, Germany, Austria, Spain

*national expansion TBC

Sources:[1]Beck et al. The Natural History of MPS I: Global Perspectives from the MPS I Registry. Genetics in Medicine 2014, 16(10), 759;
[2] https://www.raredisorders.ca/content/uploads/CORD-Submission-on-Newborn-Screening-Program-18Sep2015.pdfhttps://baebies.com/newborn-screening-for-lysosomal-storage-disorders-expands-despite-the-covid-19-pandemic/ , https://pubmed.ncbi.nlm.nih.gov/30409495/, https://pubmed.ncbi.nlm.nih.gov/32235807/, Donati et al. Italian Journal of Pediatrics 2018, 44(Suppl 2):126

Orchard therapeutics

Areas of Significant Unmet Need with Current Standard of Care

Enzyme Replacement Therapy (ERT)

HSCT (allogeneic bone marrow transplant)

HSC Gene Therapy

Limitations

- *Limited* efficacy on neurological symptoms and growth due to *inability* of enzyme to cross the blood brain barrier
- *No* patients reached the normal range for urinary GAG levels during confirmatory studies[1]
- *Chronic treatment* with significant burden on healthcare resources

- Prolongs survival, *partially* stabilizes cognitive development if treated early
- *Considerable* residual disease burden in majority of patients post transplant[2]
  - Growth still significantly affected, deviating from the reference curves[2]
  - **45%** moderate to severely impaired cognitive development at last follow-up[2]

Potential Differentiation

- Restoration of healthy microglia function via secretion and cross-correction
- Supraphysiological enzyme expression
- Emerging clinical profile
- One-time administration with the 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

Orchard therapeutics

OTL-203 for MPS-IH Clinical Data

Dr. Bobby Gaspar

CEO of Orchard Therapeutics

Orchard therapeutics

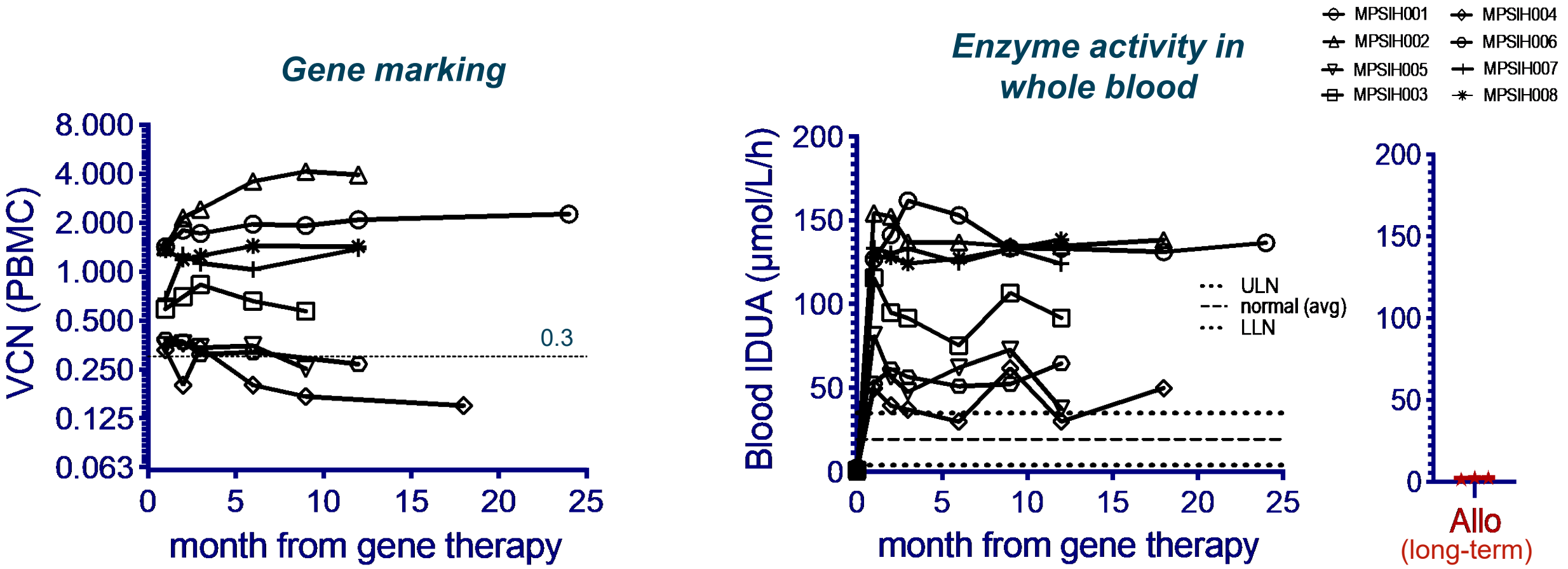
Baseline Patient and Transplant Characteristics

ID	Sex	Age at GT	DQ/IQ (baseline Bayley score)	Skeletal/ somatic phenotype	CD34+ cells/kg infused	LV vector copies per genome	Latest Follow up (Nov 2020)
001	M	24 months	75	severe	24 $x10^6$	2.1	+24 months
002	M	14 months	100	mild	14 $x10^6$	5.2	+18 months (remote)
005	M	35 months	77	severe	13 $x10^6$	1.3	+12 months (remote)
003	F	23 months	75	severe	18 $x10^6$	2.3	+12 months (remote)
004	M	14 months	95	mild	29 $x10^6$	1.0	+18 months
006	M	25 months	85	intermediate	31 $x10^6$	1.1	+12 months
007	M	20 months	80	intermediate	21 $x10^6$	3.4	+12 months
008	F	24 months	90	intermediate	20 $x10^6$	3.4	+12 months

All patients treated at less than 3 years of age with DQ/IQ score > 70

Orchard therapeutics

Stable Gene Marking and Supranormal Enzyme Expression in All Patients



All patients show above normal enzyme expression across a range of VCNs

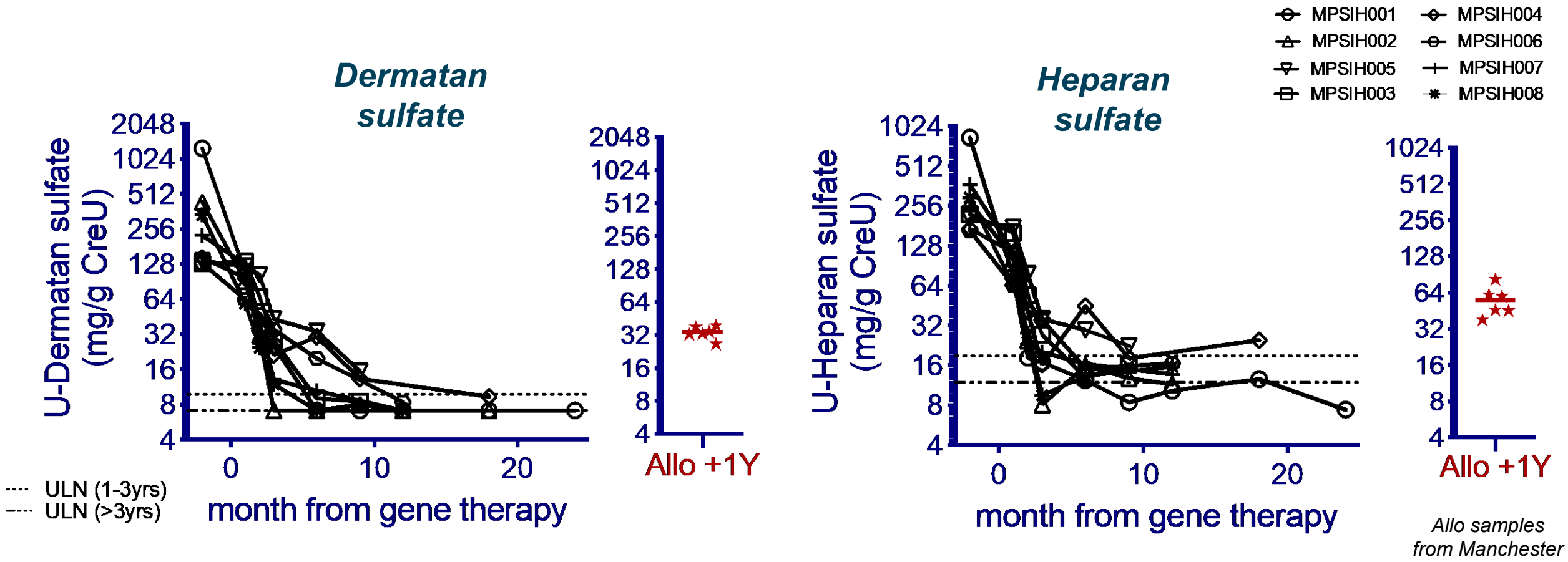
Allo samples from Monza

 VCN= Vector copy number; PBMC=peripheral blood mononuclear cell; IDUA=alpha-L-Iduronidase; Allo= Allogeneic stem cell transplant

2021 WORLDSymposium data presentation

Orchard therapeutics

Reduction and Normalization of Urinary GAG Excretion



Allo samples from Manchester

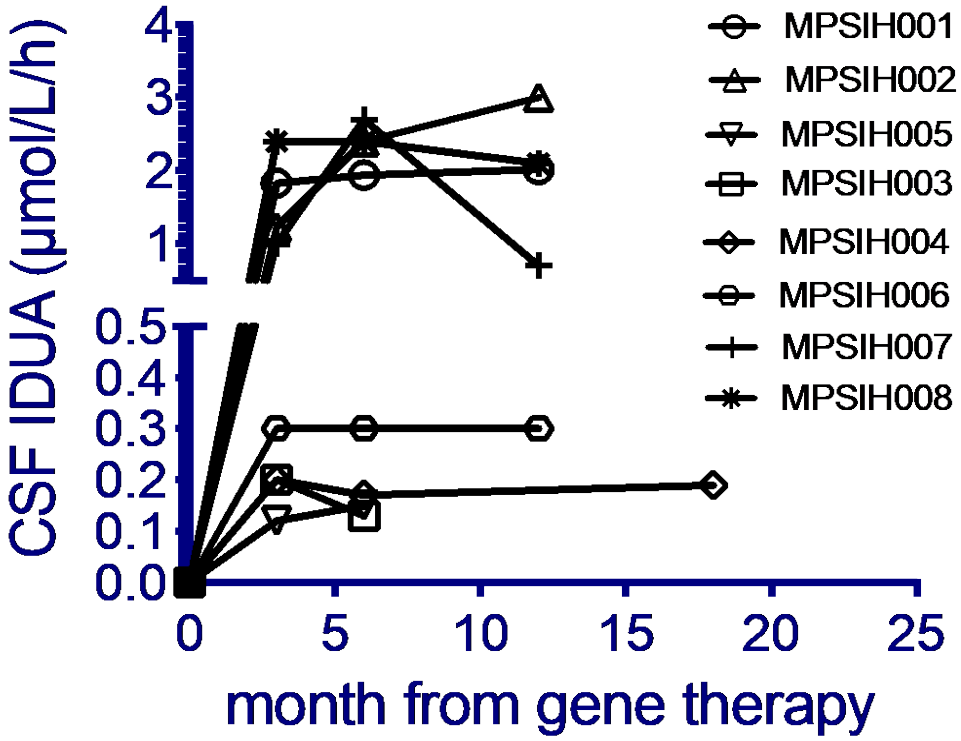
Dermatan and heparan sulfate levels reduced to normal ranges

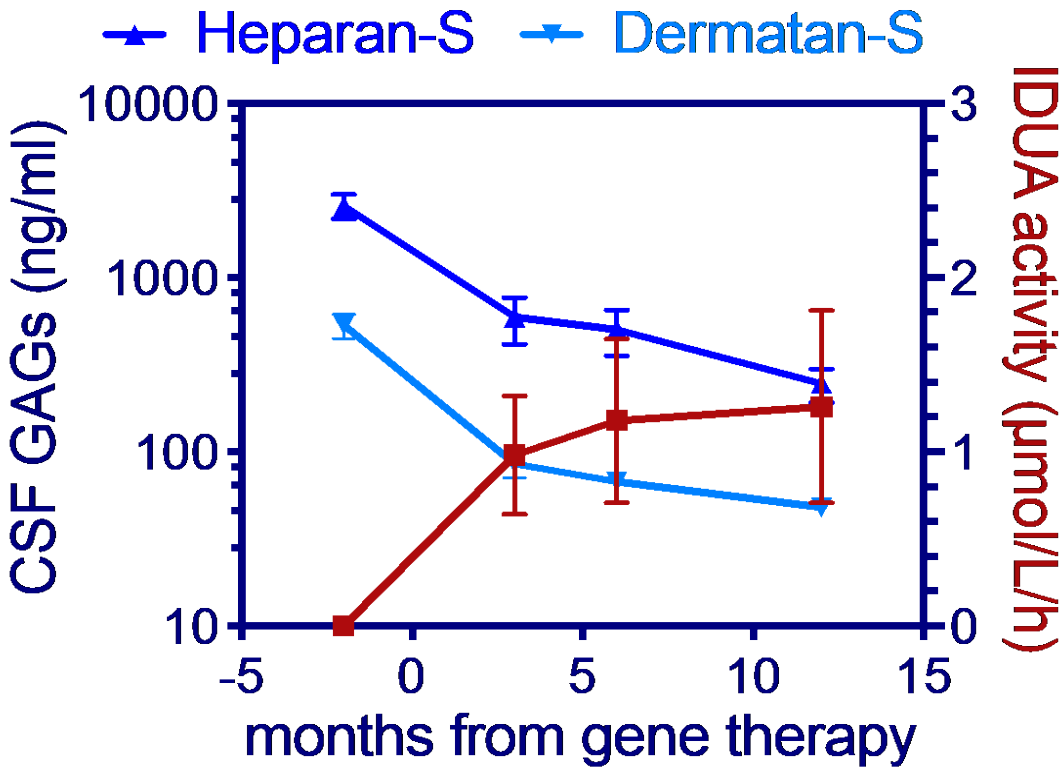
ULN= Upper or lower limit of normal; Allo= Allogeneic stem cell transplant

2021 WORLDSymposium data presentation

Orchard therapeutics

Increased IDUA Activity and GAG Reduction also Measured within the CNS



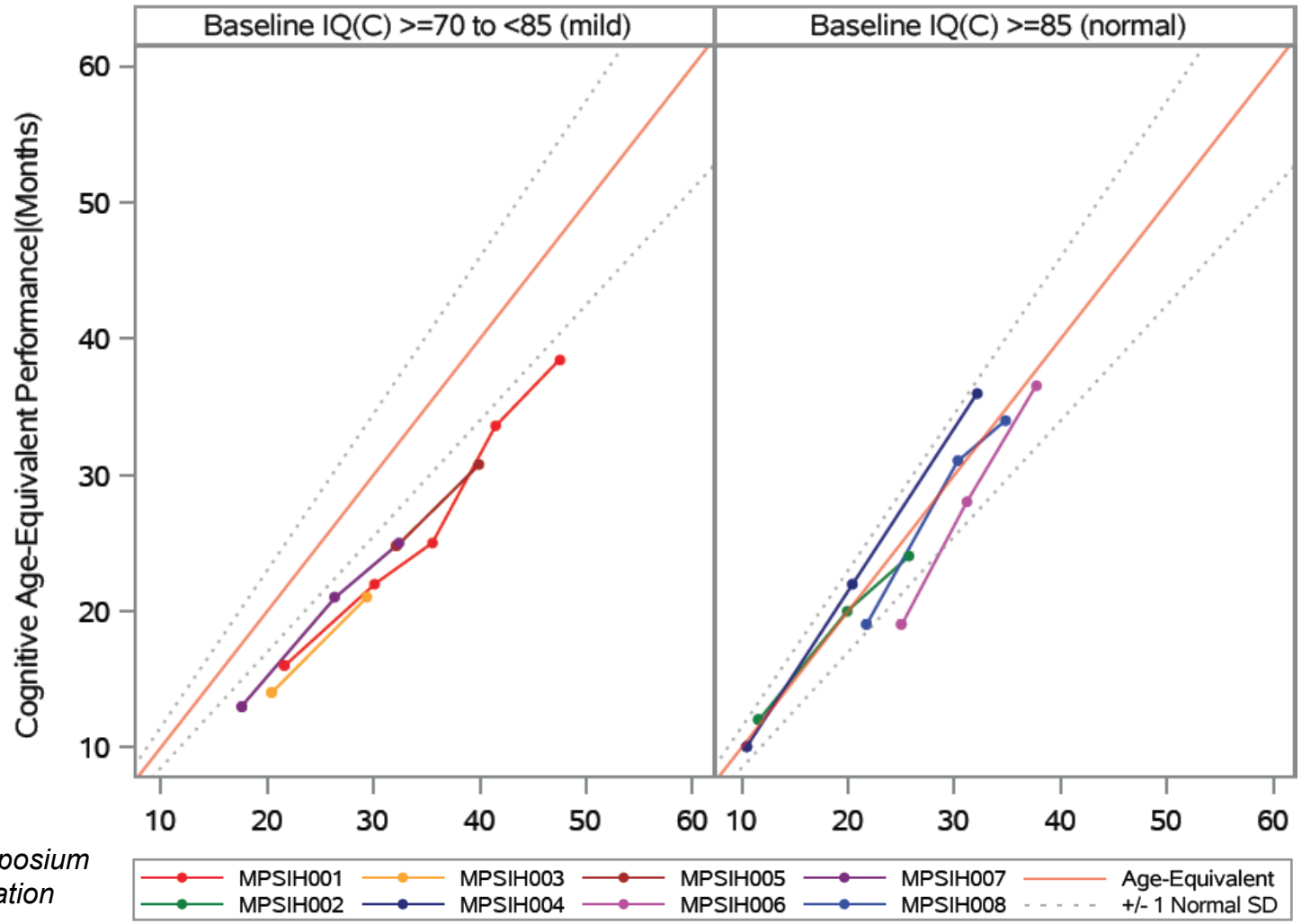


CSF= cerebral spinal fluid; IDUA=alpha-L-Iduronidase; GAG= Glycosaminoglycans;
2021 WORLDSymposium data presentation

Orchard therapeutics

All Eight Patients Showing Stable Cognitive Score vs Baseline

Cognitive Score (Bayley scale)
derived from patient IQ measures over time

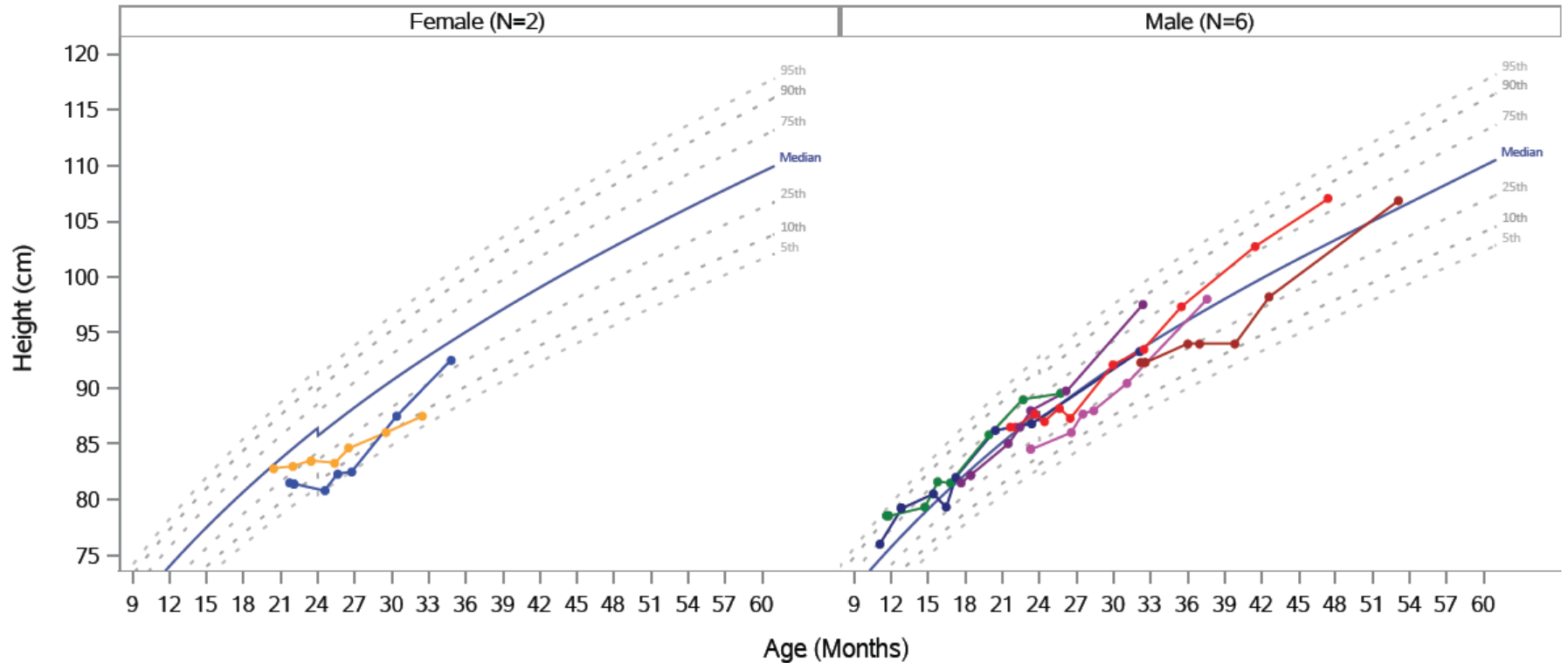


2021 WORLDSymposium data presentation

Orchard therapeutics

Improvements in Skeletal Measures Leading to Growth in Normal Range

Longitudinal Growth: normal by age



(longer follow-up needed)

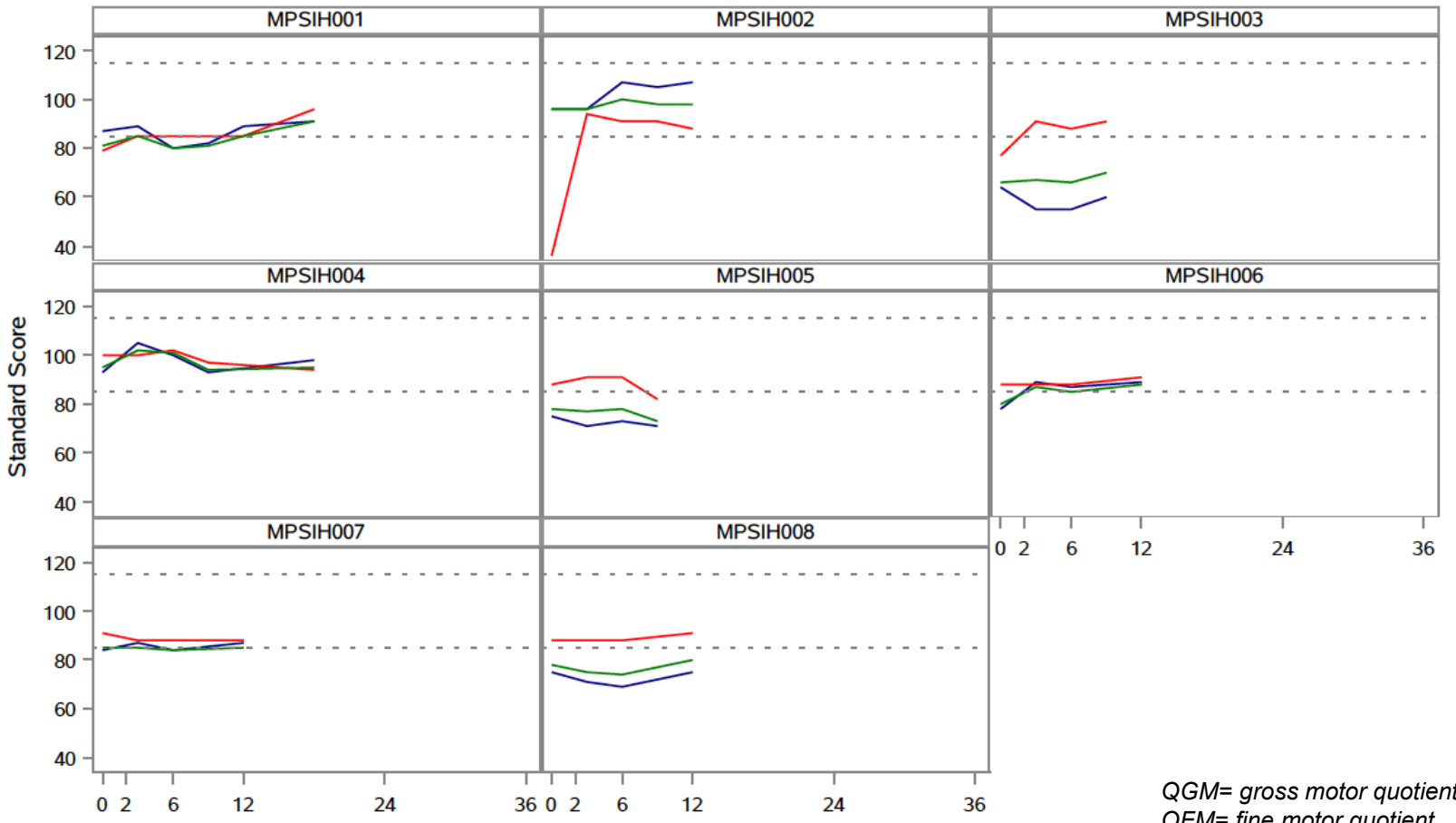
2021 WORLDSymposium data presentation

MPSIH001 MPSIH002 MPSIH003 MPSIH004
MPSIH005 MPSIH006 MPSIH007 MPSIH008

Orchard therapeutics

Stable Motor Function Seen in All Eight Patients

Stable gross and fine motor function (Peabody Developmental Motor Scale Standard Score)

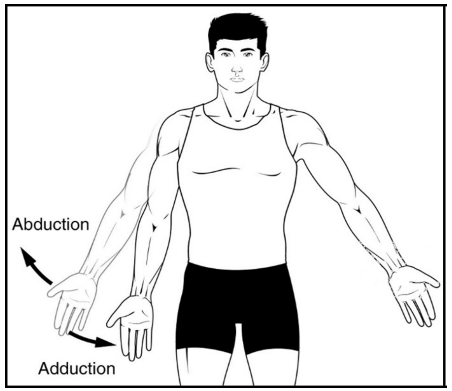


QGM= gross motor quotient
QFM= fine motor quotient
QTM= total motor quotient

2021 WORLDSymposium data presentation

Orchard therapeutics

Improved Range of Motion and Less Joint Stiffness Following Treatment

Shoulder abduction		Baseline	D90	D180	M9	M12	M18	Normal = 180°
Right	n	8	8	8	5	5	2	
	Median	**90**	**95**	**95**	**110**	**130**	**145**	
	Min	90	90	90	90	100	140	
	Max	110	150	150	150	150	150	
Left	n	8	8	8	5	5	2	
	Median	**95**	**95**	**95**	**110**	**130**	**145**	
	Min	50	90	90	90	100	140	
	Max	110	150	150	150	140	150	

D=Day; M=Month

Shoulder abduction measured at 90 degrees (mean) improves to 130 degrees (mean) at 1 year post treatment

Improvement in other range of motion measures including:

- **Shoulder flexion**
- **Knee extension**
- **Elbow extension**

Orchard therapeutics

OTL-203 (MPS-IH) Clinical Update

All patients show stable cognitive function and growth in normal range at last follow-up

Dataset Key Takeaways

- **Emerging clinical profile**
  - All patients show early clinical benefits across a range of outcomes
    - Stable cognitive function
    - Growth in normal range
    - Stable motor function
  - Follow-up out to 2 years in first patient and 6 - 18 months in remaining 7 patients
- **Continued robust biomarker data**
  - Supra-normal enzyme activity (blood IDUA) in all patients
  - Rapid normalization of substrates (urinary GAGs) sustained over time
  - Detection of IDUA activity associated with GAG clearance in the CSF

Milestones (Planned)

Clinical	Regulatory
✓ Present interim data from POC study	• Parallel scientific advice process (ongoing) • Initiate registrational study

CSF= cerebral spinal fluid; IDUA=alpha-L-Iduronidase; GAG= Glycosaminoglycans;
2021 WORLDSymposium data presentation

Orchard therapeutics

OTL-201 for MPS-IIIA Clinical Data

Dr. Simon Jones

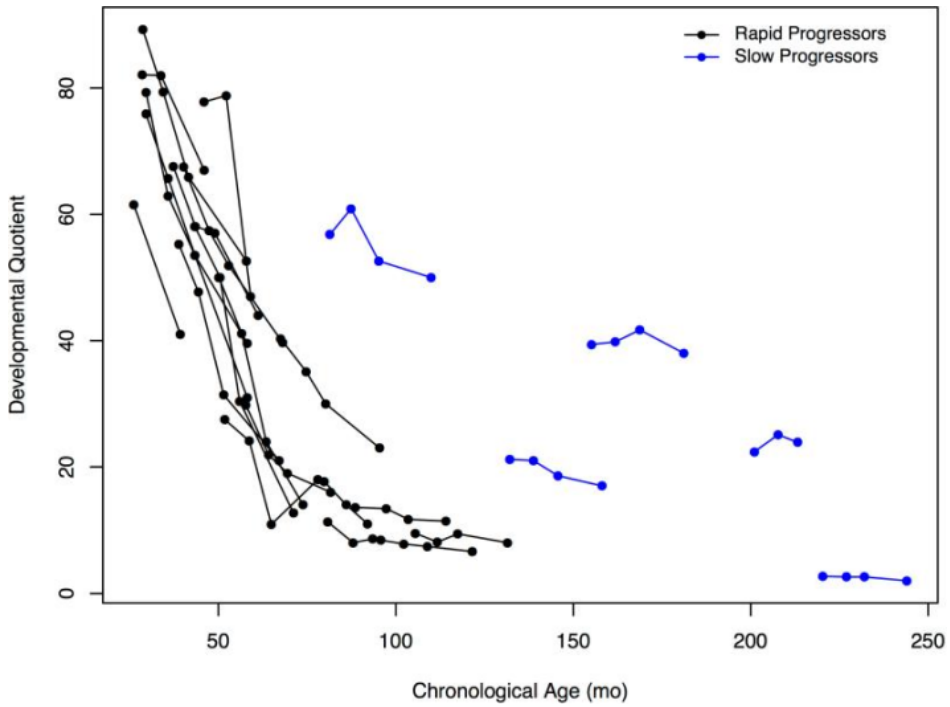
Manchester Centre for Genomic Medicine

Orchard therapeutics™

MPS-IIIA is a Progressive and Devastating Disease

- **Sanfilippo Syndrome type A**
- **Pathogenic variants in SGSH gene**
- **Substrate accumulation**
  - Heparan sulfate
- **Progressive devastating sequelae**
  - Developmental delay
  - Regression
  - Hyperactivity and sleep disturbance
  - Neurological deterioration
- **No known effective treatment**

Mucopolysaccharidosis Type IIIA



Shapiro, E. G., Nestrasil, I., Delaney, K. A., Rudser, K., Kovac, V., Nair, N., Richard Iii, C. W., Haslett, P. & Whitley, C. B. (2016). 'A prospective natural history study of mucopolysaccharidosis type IIIA', The Journal of pediatrics, 170, pp. 278-287. e4

SGSH = N-Sulfoglucosamine Sulfohydrolase

2021 WORLDSymposium data presentation

Orchard therapeutics

Four Patients Recruited Since Trial Opened

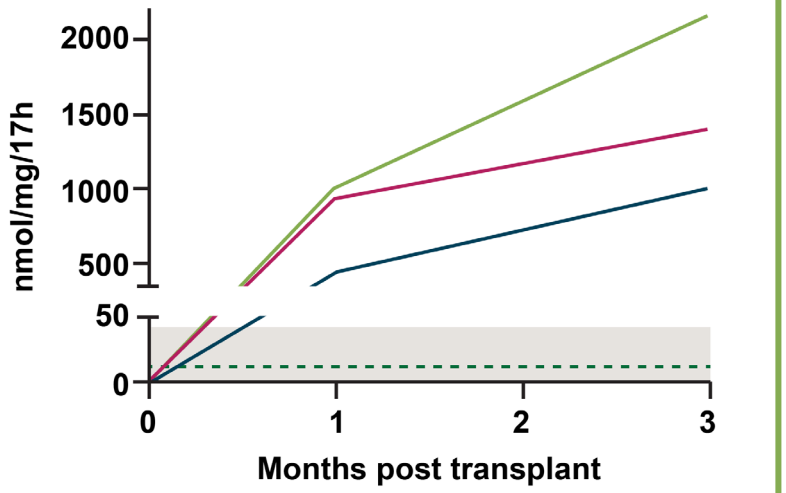
ID	Gender	Country of Referral	Age at Enrolment	Screening DQ
05-001	Female	Australia	15 months	110
05-002	Male	Germany	6 months	95
05-003	Female	Germany	20 months	105
05-004	Male	Germany	4 months	85

Hematological Engraftment in All Three Patients Treated

	05-001	05-002	05-003
Neutrophils (> 0.5 x10^9/L)	Day +13	Day +15	Day +26
Platelets (>20 x10^9/L)	Day +13	Day +29	Day +50
Hemoglobin (>80g/L)	Day +20	Day +21	Day +51

SGSH Enzyme Levels Increasing in Blood

Leukocytes



Normal Range,
3.9-42.6 nmol/mg/17hr

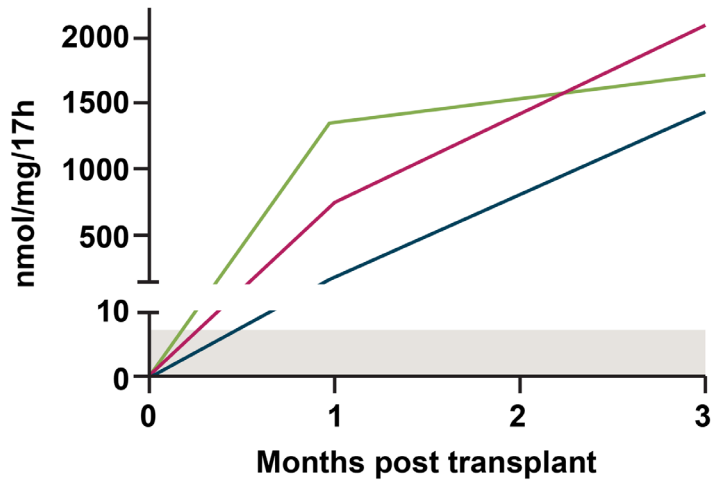
Median of Normal Range

Patient 01

Patient 02

Patient 03

CD15+ cells



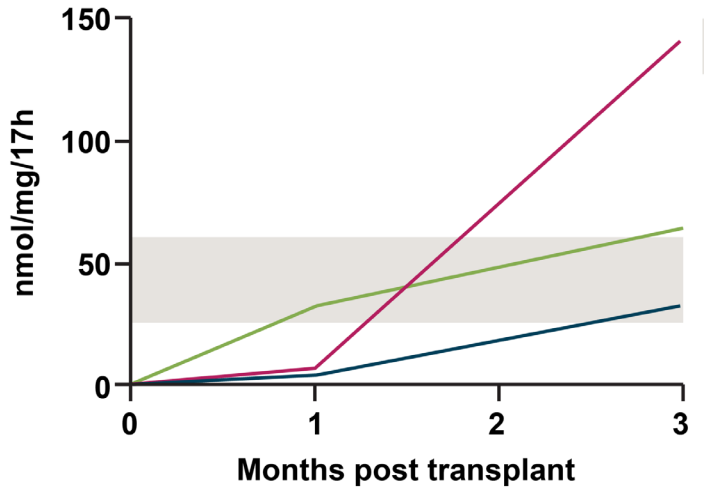
Normal Range,
1.6-7.3 nmol/mg/17hr

Patient 01

Patient 02

Patient 03

CD3+ Cells



Normal Range,
25.7-60.5 nmol/mg/17hr

Patient 01

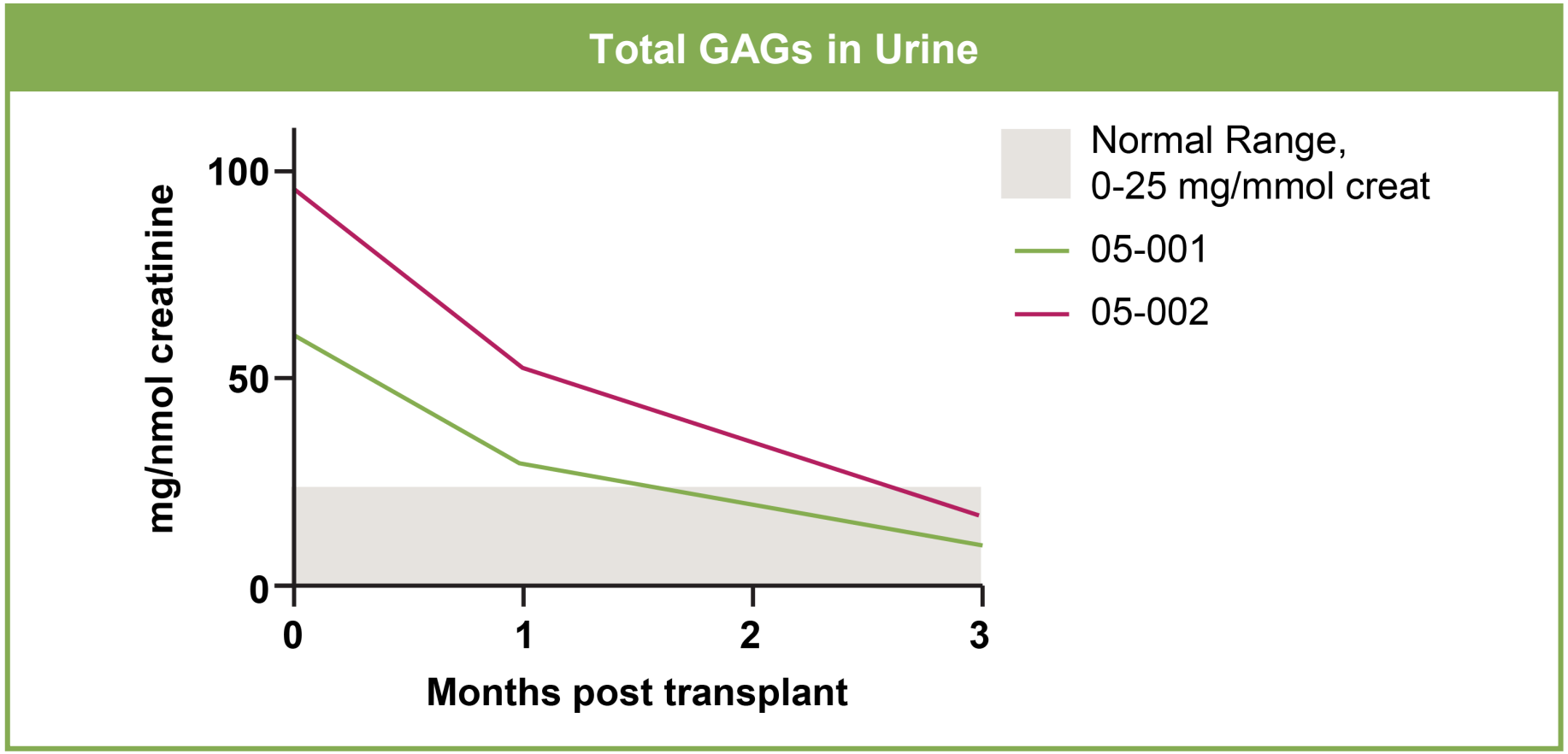
Patient 02

Patient 03

SGSH = N-Sulfoglucosamine Sulfohydrolase

2021 WORLDSymposium data presentation

Urinary GAGs Reduced to Within the Normal Range for First Two Patients



GAG= Glycosaminoglycans;
2021 WORLDSymposium data presentation

OTL-201 (MPS-IIIA): Promising Initial Biomarker Data from First 3 Patients

Dataset Key Takeaways

- Promising initial biomarker data in first 3 patients
  - Hematological engraftment in all patients
  - Supraphysiological SGSH enzyme activity in all patients
  - Substrate reduction to normal levels in first 2 patients

Clinical Milestones

- ✓ 4th POC patient enrolled
- ✓ Present interim data from POC study
- Complete POC study enrollment

SGSH = N-Sulfoglucosamine Sulfohydrolase

2021 WORLDSymposium data presentation

Orchard therapeutics

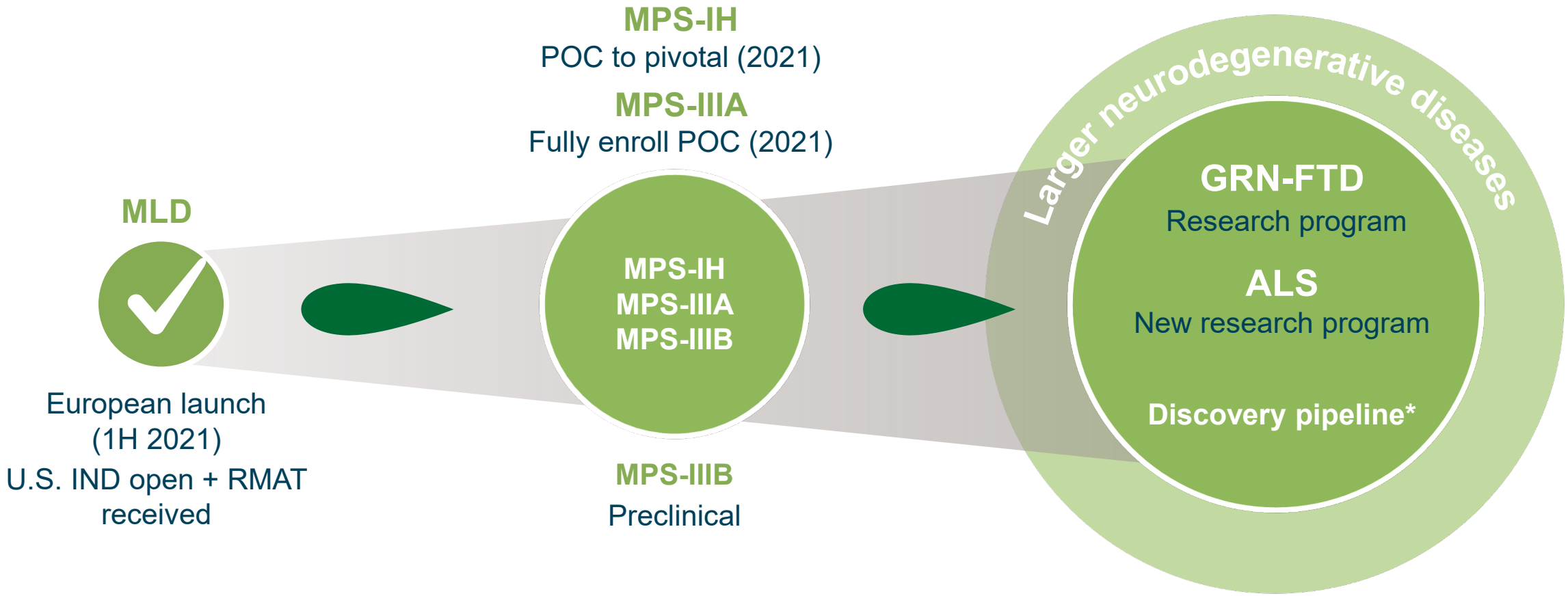
Concluding Remarks

Dr. Bobby Gaspar

CEO of Orchard Therapeutics

Orchard therapeutics™

Growing Portfolio in Neurodegenerative Disorders



*Other undisclosed development programs

Orchard therapeutics

Q&A Session

Orchard therapeutics