OTL-201
MPS-IIIA Data

IR webcast
December 12, 2022

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Forward-looking Statements

Certain information set forth in this presentation and in statements made orally during this presentation contain “forward-looking statements”. Except for statements of historical fact, information contained herein constitutes forward-looking statements and may include, but is not limited to, expectations of Orchard Therapeutics plc (the “Company” or “Orchard) regarding: (i) the safety and efficacy of Libmeldy and its product candidates; (ii) the Company’s ability to establish the infrastructure necessary to enable the treatment of eligible MLD patients and the adequacy of the Company’s supply chain and ability to commercialize Libmeldy; (iii) the expected development of the Company’s business and product candidates; (iv) the timing of regulatory submissions for approval of its product candidates; (v) the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates; (vi) the timing of announcement of preclinical 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; (vii) the timing and likelihood of approval of such product candidates by the applicable regulatory authorities; (viii) the adequacy of the Company’s supply chain, manufacturing capacity and plans for future investment and commercialization; (ix) execution of the Company’s vision and growth strategy, including with respect to global growth; (x) the size and value of potential markets for and commercialization of Libmeldy and the Company’s product candidates; and (xi) expected financial performance and financial condition, including its cash runway. 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.

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ASH IR Event Agenda

AGENDA TOPIC		SPEAKER
Orchard's HSC Gene Therapy and MPS-IIIA Disease Overview		**Bobby Gaspar, M.D. Ph.D.** *Orchard CEO*
OTL-201 ASH Update: Biochemical Data		**Prof. Rob Wynn** ***Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust***
OTL-201 ASH Update: Clinical Data		**Dr. Simon Jones** *Manchester Centre for Genomic Medicine*
Q&A	   	**Leslie Meltzer, Ph.D.** *Orchard CMO*

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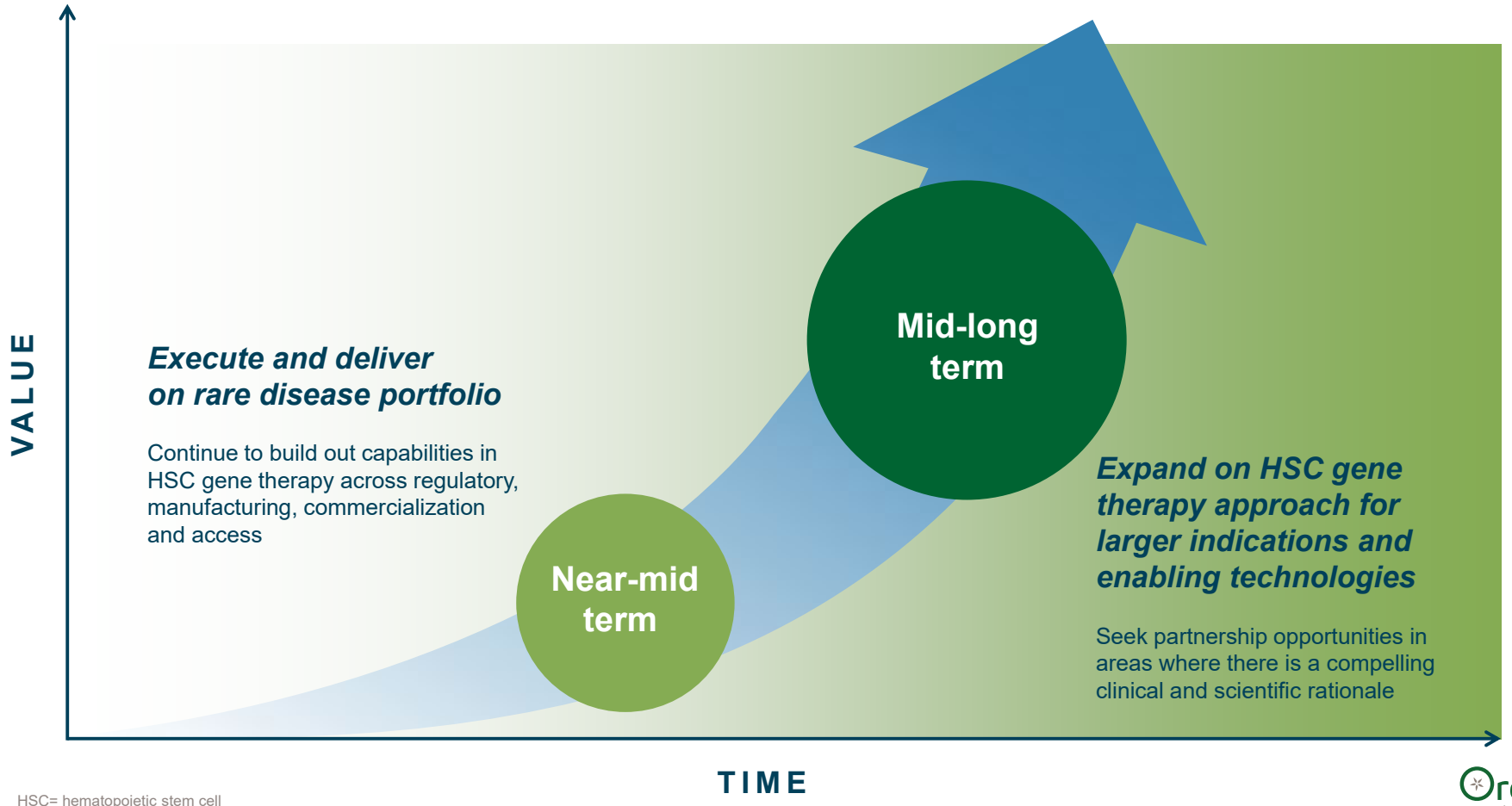
Orchard's Vision for Severe Genetic Diseases



HSC= hematopoietic stem cell

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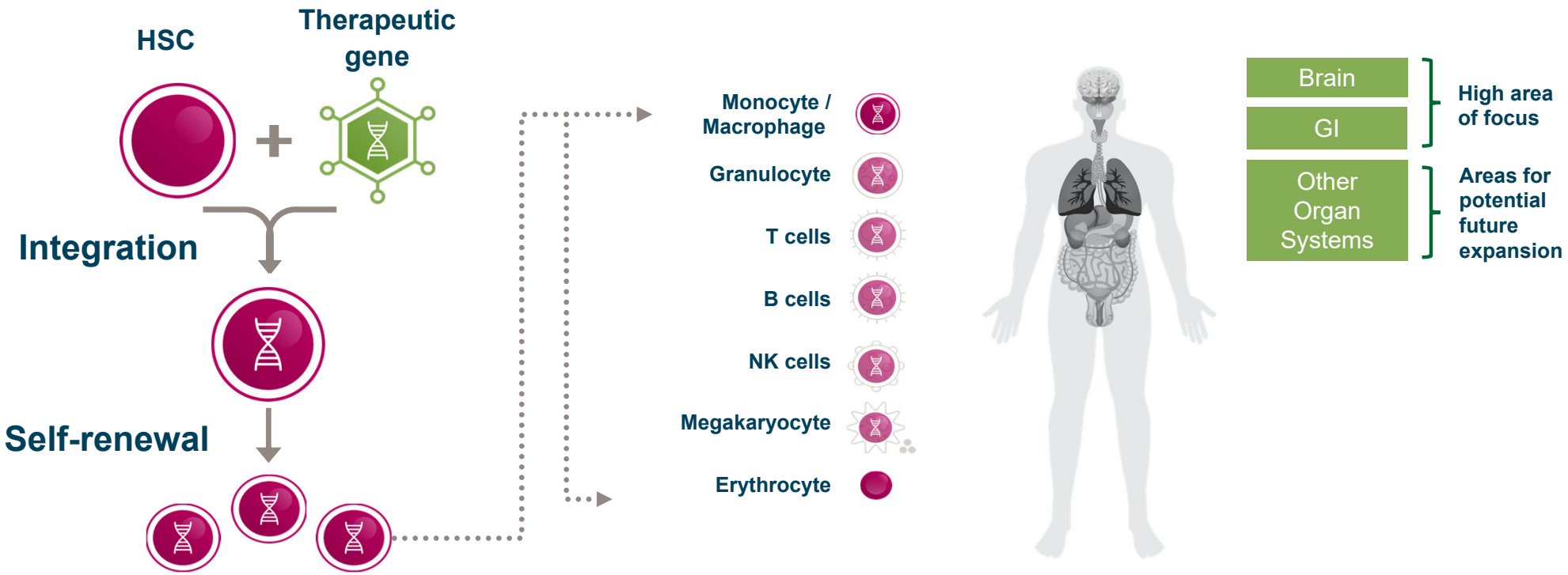
HSC Gene Therapy Offers a Highly Differentiated Approach



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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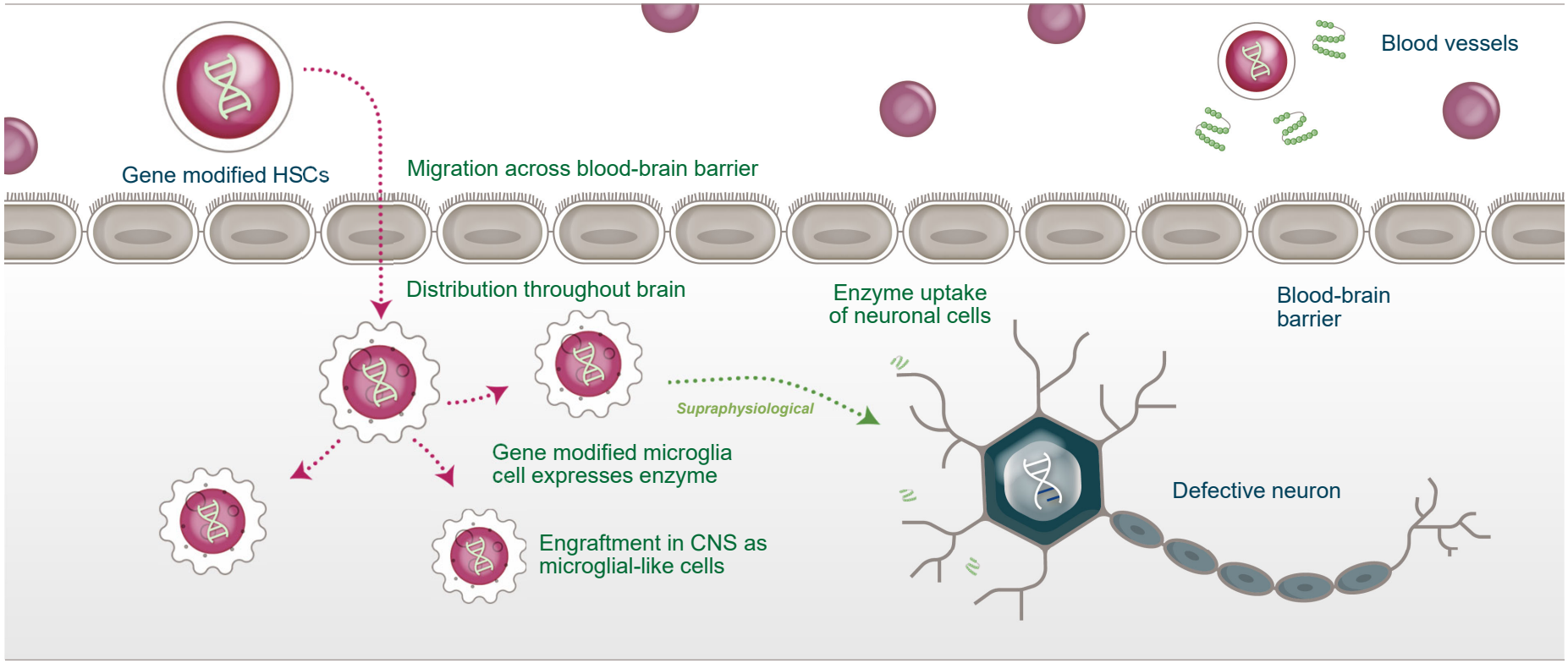
Delivering Proteins to Brain

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



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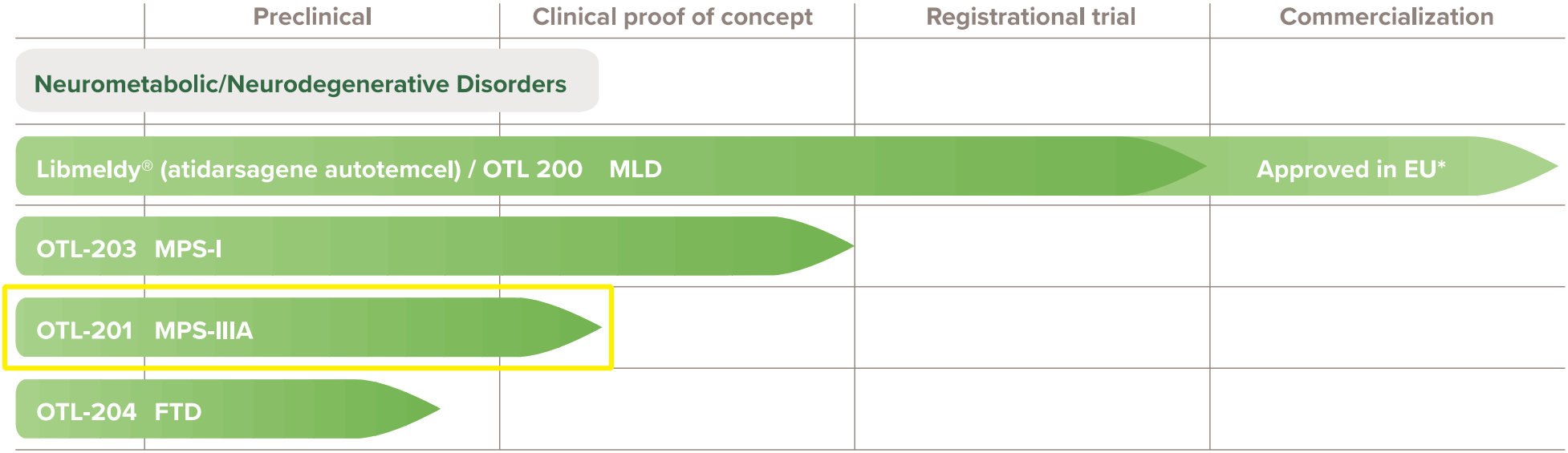
Robust Pipeline in Neurodegenerative Disorders



Several additional research and preclinical programs under development.

*Libmeldy® is approved in the European Union, UK, Iceland, Liechtenstein and Norway. In the U.S., OTL-200 is an investigational therapy. All other therapies in our pipeline are investigational and have not been approved by any regulatory agency or health authority.

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First Clinical Outcomes from OTL-201 POC Study

- **5 patients treated between 6 – 24 months of age**
- **Median 1.5 years follow-up (range 9 – 24 months)**

- **No evidence of insertional oncogenesis or clonal dominance**
- **Robust, sustained hematological engraftment**
- **Supraphysiological levels of SGSH enzyme + normalization of heparan sulfate substrate levels**

- **Gain of cognitive skills in line with normal development in 4 patients with 1 patient showing marked improvement compared to natural history at 18 months of follow-up**
  - Evidenced by acquisition of speech, continence, complex play requiring concentration
  - Longer follow-up required to assess outcomes

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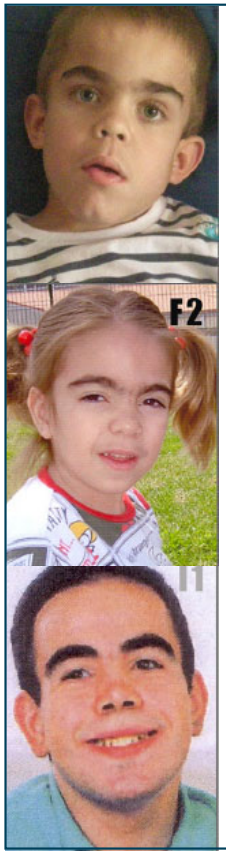
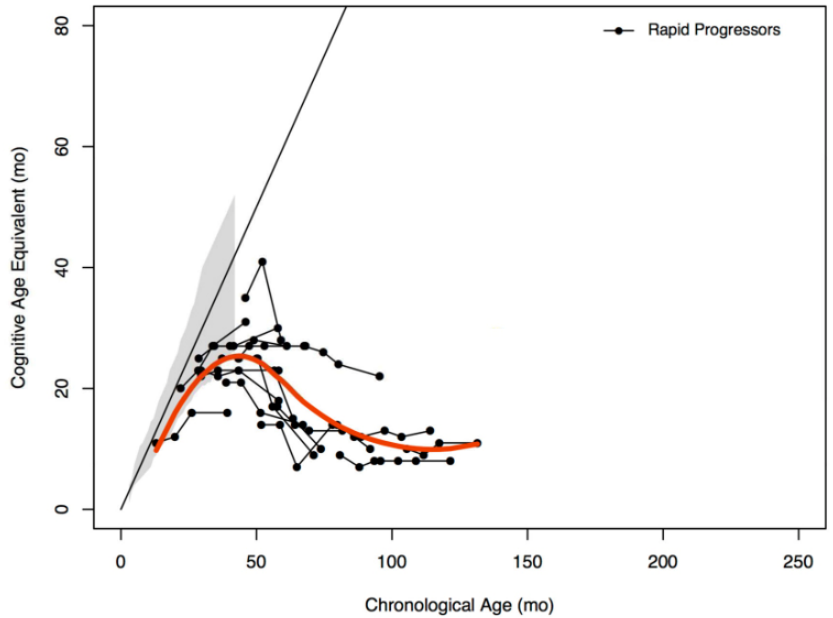
MPS-IIIA is a Progressive and Devastating Disease

- **Sanfilippo Syndrome type A**
- Pathogenic variants in ***SGSH* gene**
- Accumulation of **substrate heparan sulfate**
- **Severe CNS degeneration** w/ somatic manifestations
- **Severe phenotype** – development slows from 24 months of age, followed by cognitive decline, behavioural disturbances, loss of skills and eventual death
- **No successful treatment options** – allogeneic HSCT shows ***no modification*** of disease phenotype despite wild type donor, full engraftment and early treatment
- **Incidence: ~1 in 100,000 live births**





SGSH = N-Sulfoglucosamine Sulfohydrolase
Shapiro EG, et al. J Pediatr 2016;170:278-87.
Photos adapted from Natural History of Sanfilippo Syndrome in Spain; Orphanet Journal of Rare Diseases · December 2013

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High Unmet Medical Need in MPS-IIIA with Supportive Care as Only Standard of Care

Limitations

Enzyme Replacement Therapy (ERT)

- *No approved ERT* due to inability of enzyme to cross the blood brain barrier

Allogeneic HSCT (allogeneic bone marrow transplant)

- *No effect on disease phenotype* despite wild type donor, full engraftment and early treatment

AAV approaches (direct intracerebral injection or IV infusion)

- Robust correction of neurocognitive decline *not established*
- Safety profile for direct intracerebral injection *not established*
- Durability profile with one-time administration *not established*
- Some patient eligibility restrictions due to presence of *anti-AAV antibodies*
- Generation of host *immune responses* to systemic infusion

Potential Differentiation

Autologous HSC Gene Therapy

- Restoration of healthy microglia function via **secretion and cross-correction**
- **Supraphysiological enzyme expression**
- Favorable benefit / risk profile in MLD and CCALD with **two approved products**
- **One-time administration** with the potential for **long-term durability**

Valstar MJ, et al. J Inherit Metab Dis 2008;31:240-252; Sun K, et al. J Clin Pharmacol 2022;62;S79-S94

Fumagalli F, et al. Lancet 2022;399(10322):372-383

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OTL-201 Study Background and Biochemical Data

Professor Rob Wynn

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OTL-201 POC Study Design

- A phase I/II study of autologous CD34^{+} haematopoietic stem cells transduced *ex vivo* with CD11b lentiviral vector encoding for human *SGSH* (OTL-201) in patients with MPS-IIIA
- Investigator-led trial; NCT04201405; Sponsor: University of Manchester
- **Key Inclusion Criteria:** ≥ 3 months to ≤ 24 months, DQ ≥ 80 and rapidly progressive MPS-IIIA phenotype/genotype
  - Phenotypes independently assessed/confirmed by independent metabolic expert prior to enrollment through review of genotype, family history, biochemistry, and physical examination
- 36-month follow-up
- No untreated/placebo/comparator patients included for ethical reasons (no standard of care)

Primary Objectives

- To evaluate the safety and tolerability of the IMP
- To evaluate biological efficacy of the IMP post-treatment via SGSH activity in total leukocytes

Secondary and Exploratory Objectives

- Overall Survival
- Peripheral engraftment
- Efficacy on cognitive function
- Impact on behavior, adaptive function, QoL and family
- Heparan sulfate in CSF, plasma and urine
- SGSH in CSF, plasma, PBMCs and subpopulations

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OTL-201 POC Patient Recruitment

Patient	Gender	Country of Referral	Age at treatment	Gene Variant	Screening DQ	Completed follow up to date	IMP dose at transplant $CD34^+$ $x10^6$/kg	VCN of IMP
05-001	Female	Australia	18.3 months	c.364G>A (p.Gly122Arg)	110	24 months	9.28	3.54
05-002	Male	Germany	8.6 months	c.1167C>A (p.Asn389Lys)	95	18 months	22.7	3.23
05-003	Female	Germany	23.3 months	c.734G<A (p.Arg245His) c.1297c>T (p.Arg433Trp)	105	18 months	7.67	6.26
05-004	Male	Germany	6.2 months	c.734G>A (p.Arg245His) c.1429G>A (P.Asp477Asn)	85	12 months	17.84	8.91
05-006	Male	Hong Kong	23.6 months	compound heterozygous: c.466G>T; 1298G>A (p.Gly149Val Arg433Gln)	85	9 months*	4.37	(1) 1.19 (2) 3.36

2022 ASH Annual Meeting
DQ = Developmental Quotient; IMP = Investigational medicinal product; VCN = vector copy number
All patients with the exception of patient 003 had an older affected sibling
*Patient 006 had month 12 assessments performed at month 9 follow-up visit
A specials patient was treated **before** commencement of the trial outside of age inclusion and is not on the trial protocol.

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Rapid and Robust Engraftment

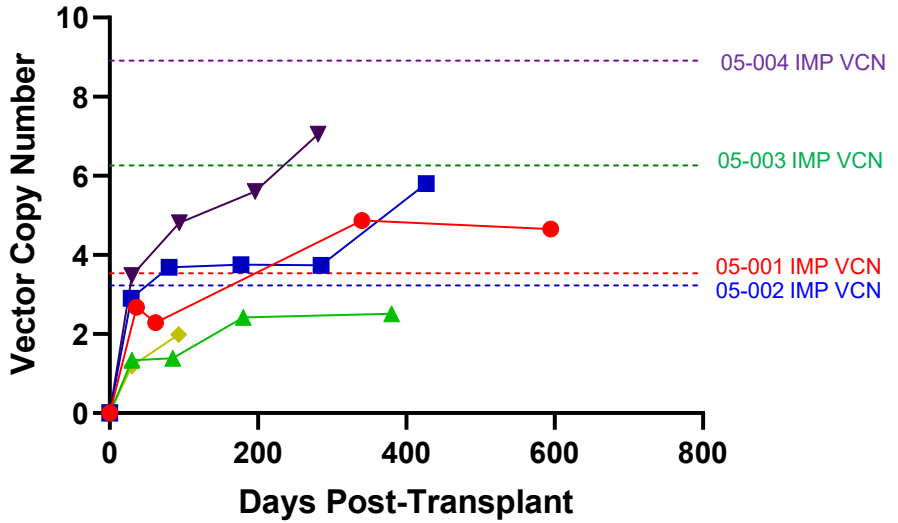
Engraftment was rapid:

- neutrophil engraftment, median: 19 days
- platelet engraftment, median: 28 days
- red blood cell engraftment, median: 25 days

No evidence of clonal expansion

No deaths or evidence of insertional oncogenesis

Vector Copy Number (VCN) in Leukocytes



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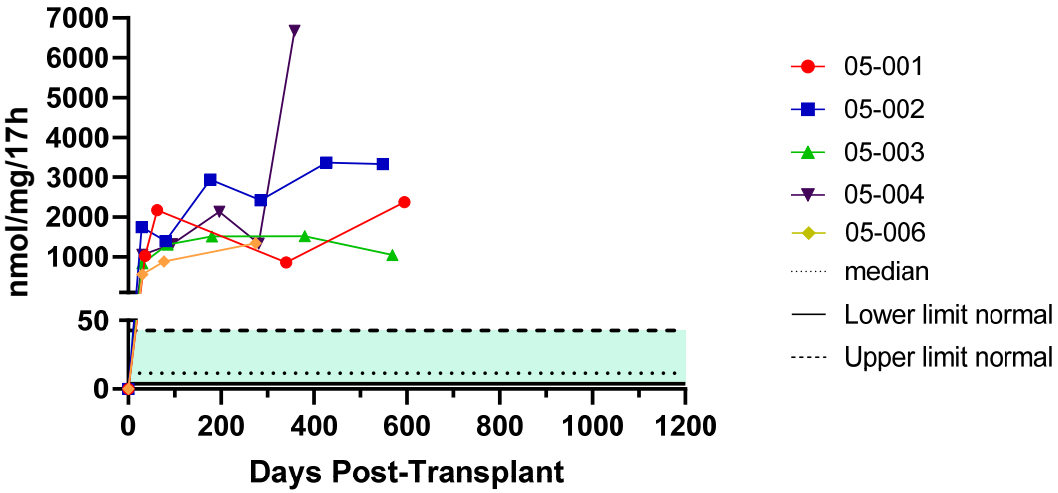
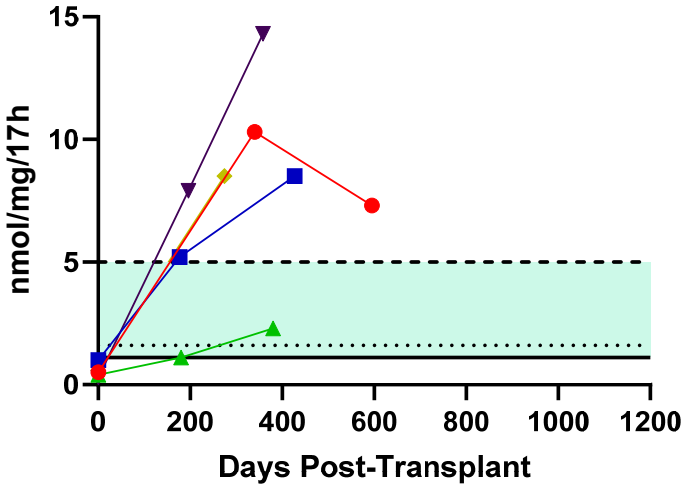
SGSH Enzyme Activity – Increase in CNS and periphery

SGSH Activity in Leukocytes



Supraphysiological SGSH levels were detected at one month post-GT through last follow-up

SGSH Activity in CSF



CSF SGSH levels were within or above normal range at 6 months to last follow-up

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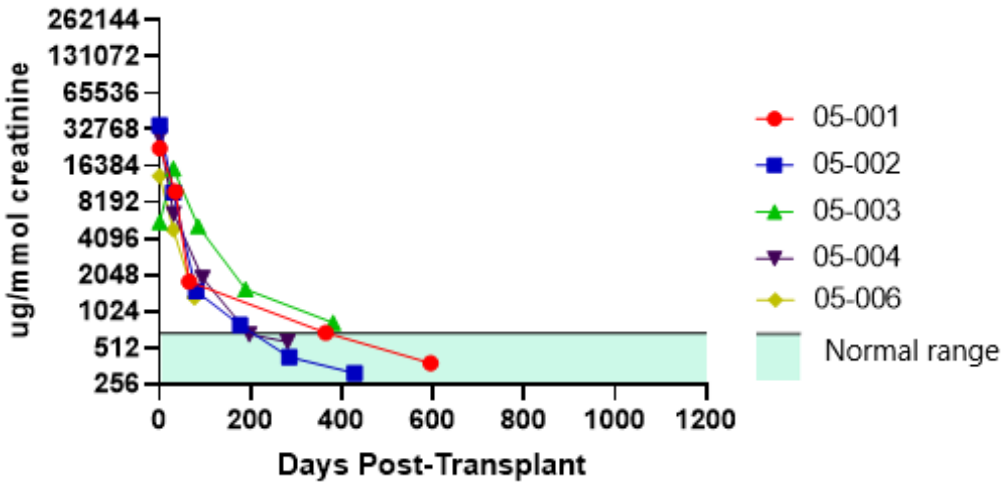
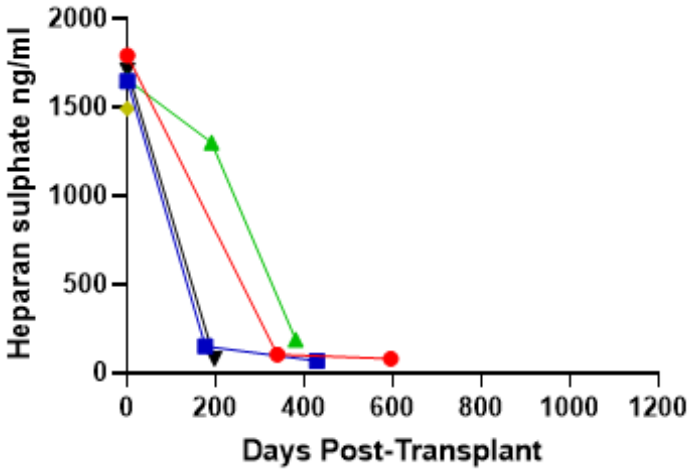
Heparan Sulfate Levels – Reduction in CNS and periphery

Urine HS Levels



CSF HS Levels



Rapid decreases from baseline of heparan sulfate in urine and CSF were seen in all evaluated patients.
Reduction in CSF HS has never been achieved with allogeneic HSCT.

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OTL-201 Clinical Outcomes

Dr. Simon Jones

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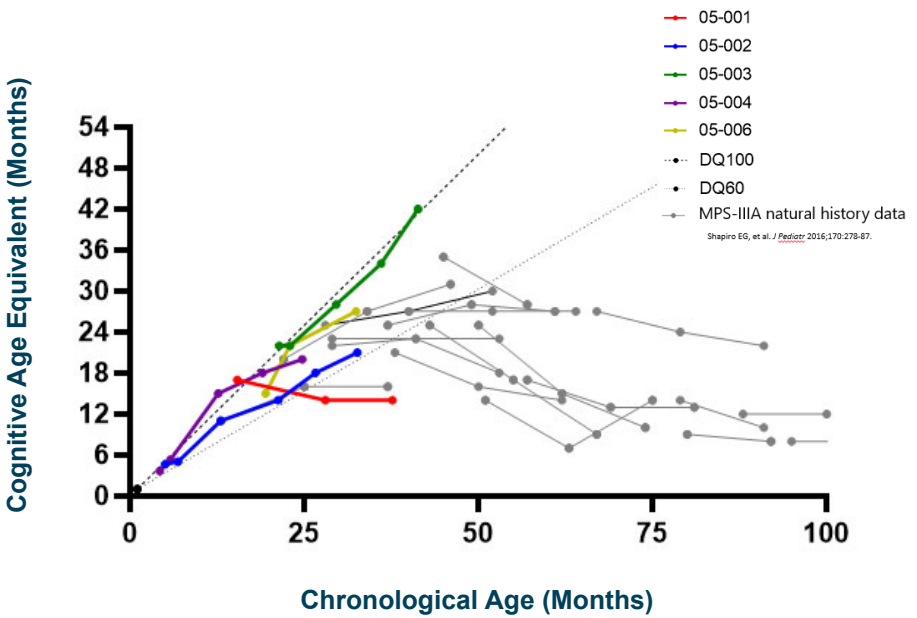
Neurocognitive Outcomes

- 4 / 5 patients are demonstrating **gain of cognitive skills in line with development in healthy children**
- Demonstration of developmental skill acquisition and behavioral phenotype not typically seen in untreated MPS-IIIA patients
- Acquisition of speech, continence and complex play requiring concentration engaged
- Longer follow-up is needed to further assess these outcomes and is ongoing

Developmental Age Equivalent



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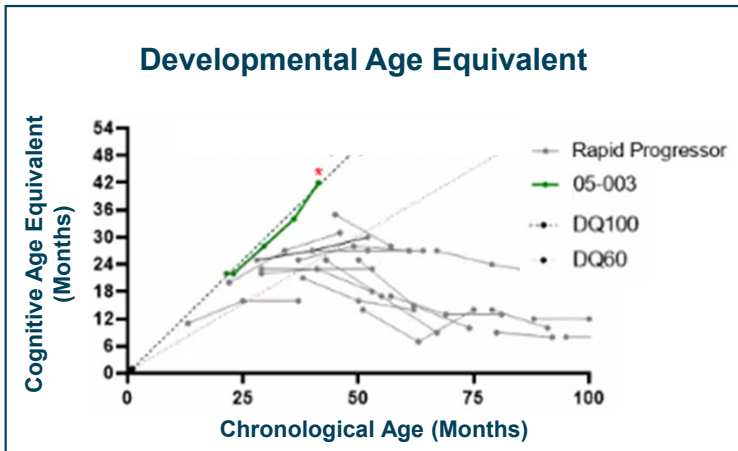
Patient 003 Summary

Pre-treatment with GT	Post GT Treatment

Patient 003 reached the ceiling of the Bayley scale and progressed onto the Kaufman assessment – first MPS-IIIA patient with rapidly progressive phenotype at Manchester that has completed the Kaufman assessment



*Exceeded Bayley at 18 month visit– 24+ month visit not shown

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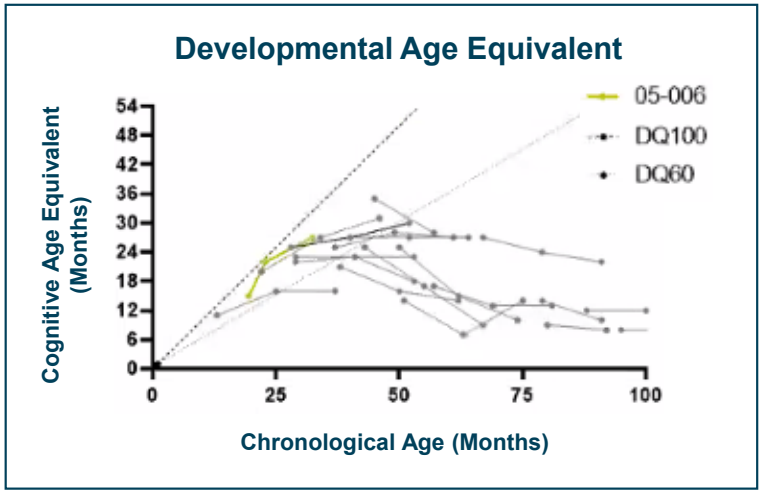
Patient 006 Summary

Post GT Treatment

Patient 006 engaged in complex tasks and able to wear glasses and a mask



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OTL-201 POC Conclusions

- ✓ Treatment was generally well-tolerated
- ✓ Robust, prompt, sustained, multi-lineage engraftment of genetically modified cells
- ✓ Supra-physiological levels of SGSH enzyme in leukocytes, plasma and CSF
- ✓ Rapid and significant reduction of substrate observed in all compartments
- ✓ Neurocognitive trial data is early but suggests a modification of the neurological phenotype in patients

OTL-201 Program Next Steps

- Report additional biochemical and clinical outcomes
- Patients will be followed for a minimum of 3 years
- Significant medical need given there are no effective therapies
- Program presents multiple development and commercial synergies with Orchard's other neurometabolic programs

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Q&A Session