UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 12 , 2022

ORCHARD THERAPEUTICS PLC
(Exact name of Registrant as Specified in Its Charter)

England and Wales	**001-38722**	**Not Applicable**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

245 Hammersmith Road
London W6 8PW
United Kingdom
(Address of Principal Executive Offices; Zip Code)

Registrant's Telephone Number, Including Area Code: +44 (0) 203 808 8286

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
American Depositary Shares, each representing one ordinary share, nominal value £0.10 per share	ORTX	The Nasdaq Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On December 12, 2022, Orchard Therapeutics plc (the "Company") presented at the 64th American Society of Hematology (ASH) Annual Meeting & Exposition in New Orleans, Louisiana and intends to host a conference call and webcast to review the data presented at the meeting. A copy of the Company's slide presentation is being furnished as Exhibit 99.1 to this Current Report on Form 8-K (the "Report"). The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.1.

The information contained in Item 7.01 of this Report and Exhibit 99.1 attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events.

On December 12, 2022, the Company issued a press release titled "Orchard Therapeutics Announces Promising Early Neurocognitive Outcomes from Ongoing Proof-of-concept Study of OTL-201 in MPS-IIIA." A copy of the press release is attached as Exhibit 99.2 to this Report and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	Description
99.1	Presentation of Orchard Therapeutics plc
99.2	Press release, dated December 12, 2022
104	Cover page interactive data file (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ORCHARD THERAPEUTICS PLC

Date: December 12, 2022

By: /s/ Frank E. Thomas
Frank E. Thomas
President and Chief Operating Officer

OTL-201
MPS-IIIA Data

IR webcast
December 12, 2022

Orchard therapeutics™

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.

These statements are neither promises nor guarantees of future performance. Such forward-looking statements necessarily involve known and unknown 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. In particular, these risks and uncertainties include, without limitation, the risk that Libmeldy will not be successfully commercialized, including the risk that the Company may not secure adequate pricing or reimbursement to support continued development of Libmeldy or its product candidates, if approved; the risk that any one or more of the Company’s product candidates, including OTL-200, will not be approved, successfully developed or commercialized; the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical studies or clinical trials of Orchard’s product candidates will not be repeated or continue in ongoing or future studies or trials involving its product candidates; the risk that the market opportunity for Libmeldy or its product candidates may be lower than estimated; the risks from high inflation, macroeconomic conditions and geopolitical instability; and, the severity of the ongoing and evolving impact of the COVID-19 pandemic on Orchard’s business, including on preclinical and clinical development, its supply chain and commercial programs. You are cautioned not to place undue reliance on forward-looking statements. For additional disclosure regarding these and other risks faced by the Company, see the disclosure contained in the Company’s most recent annual or quarterly filed with the U.S. Securities and Exchange Commission (the “SEC”), 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.

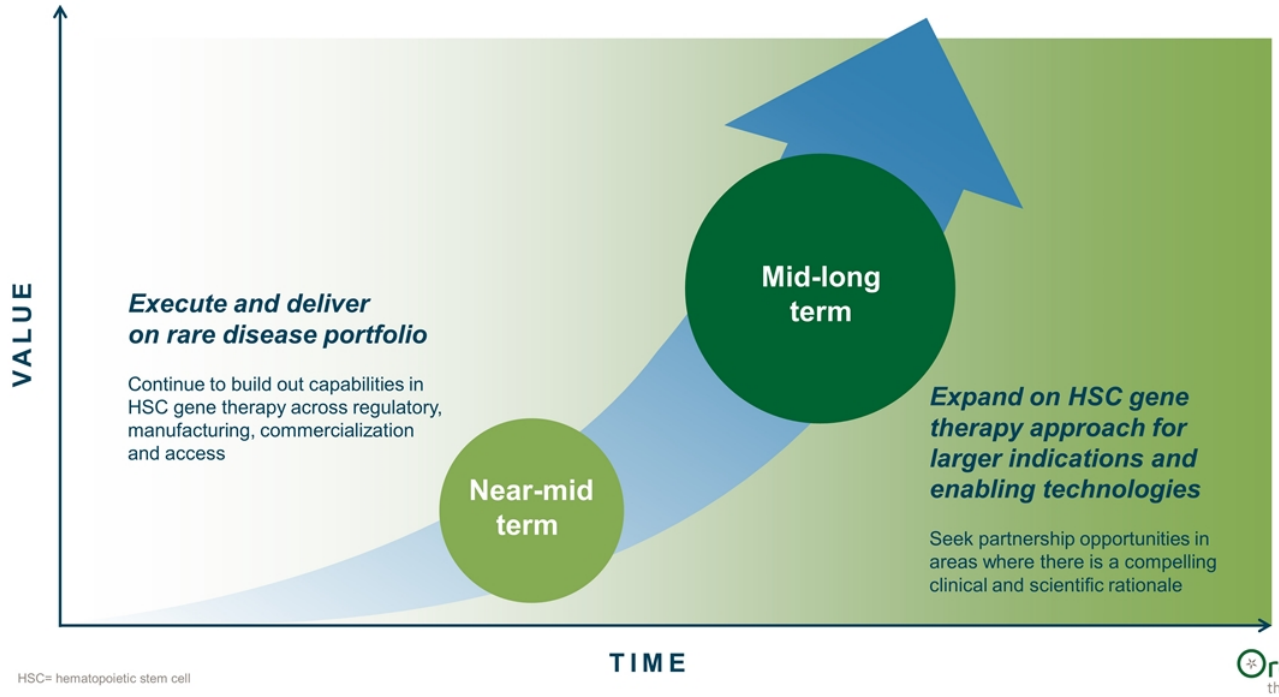
Orchard therapeutics

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*

Orchard therapeutics

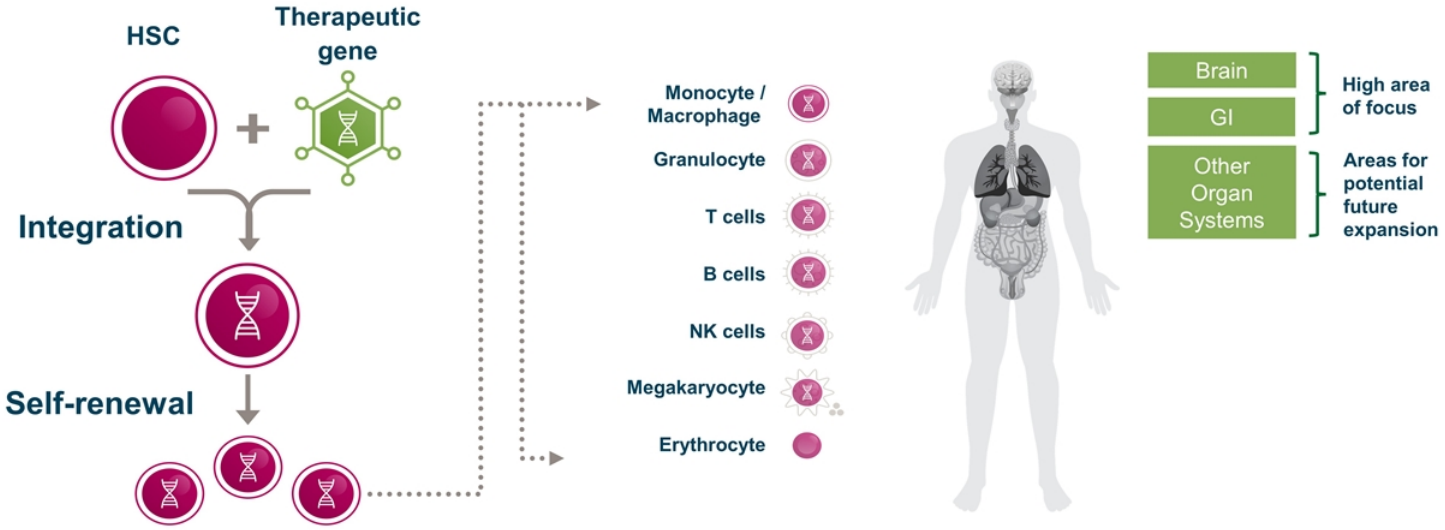
Orchard's Vision for Severe Genetic Diseases



HSC= hematopoietic stem cell

Orchard therapeutics

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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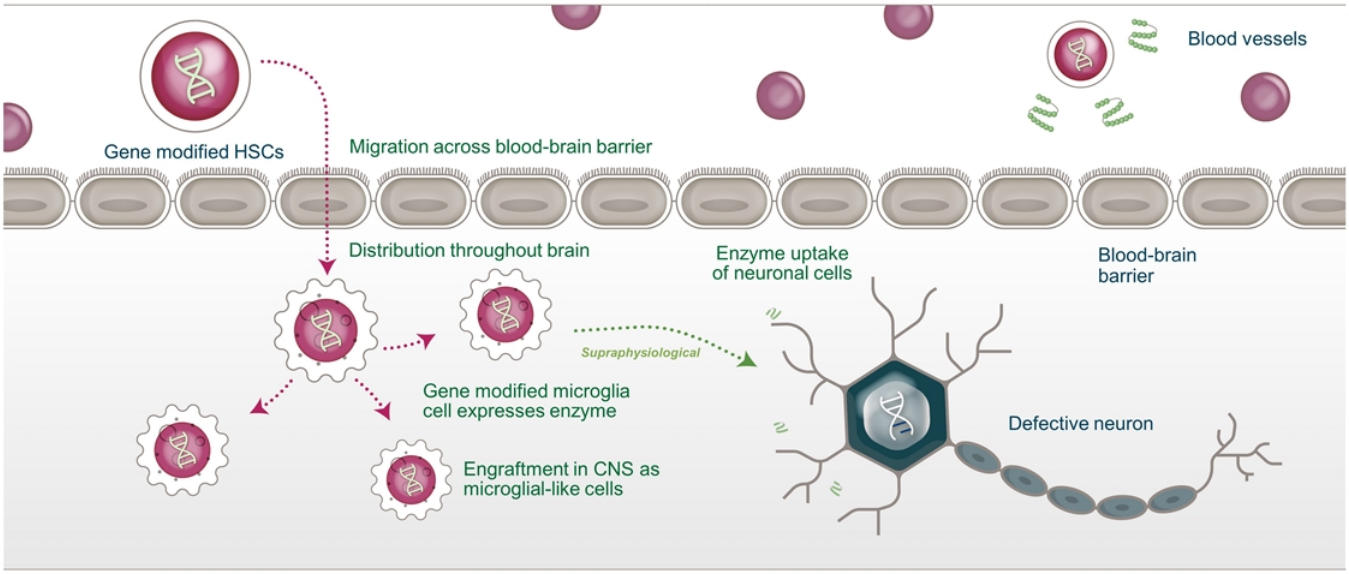
Delivering Proteins to Brain

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



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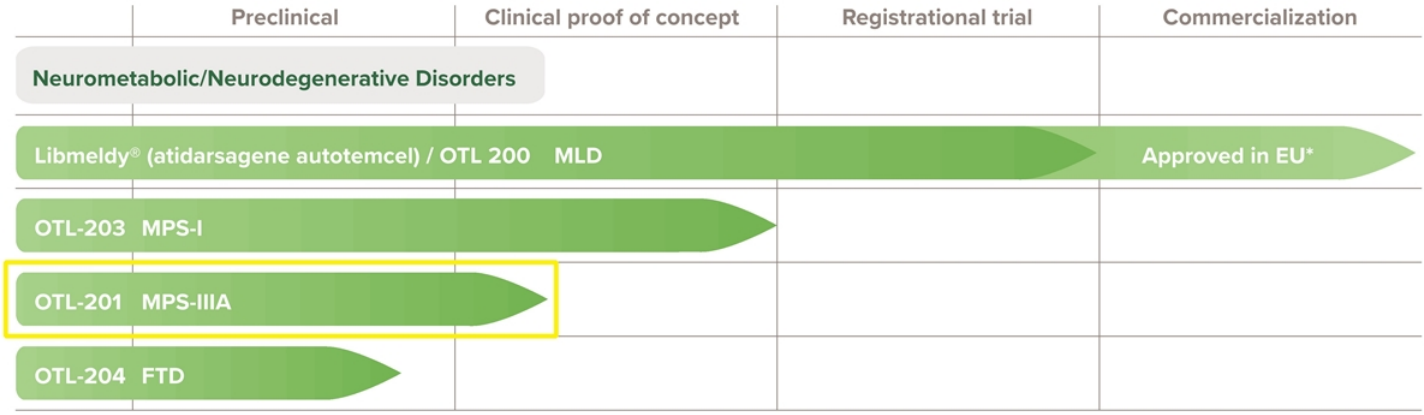
Robust Pipeline in Neurodegenerative Disorders



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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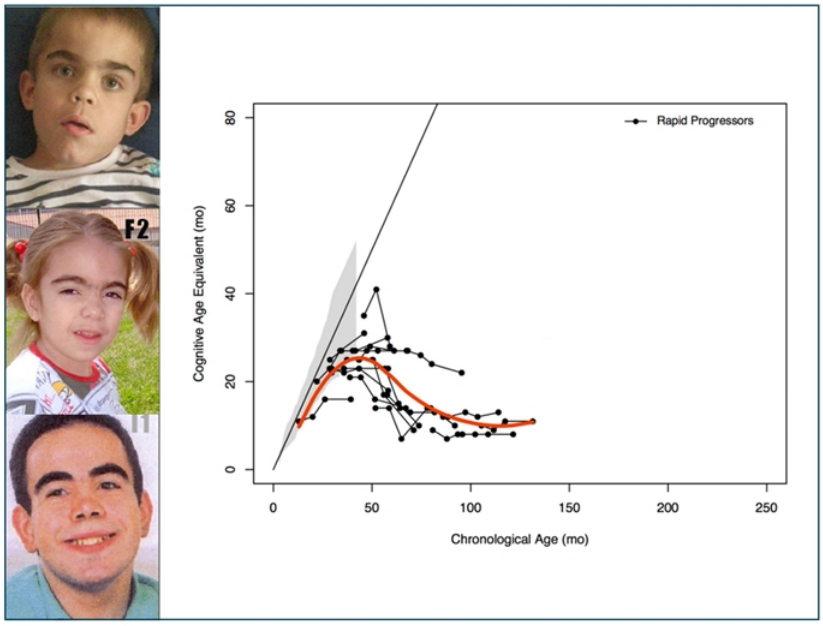
MPS-IIIA is a Progressive and Devastating Disease

- **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

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

Orchard therapeutics

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

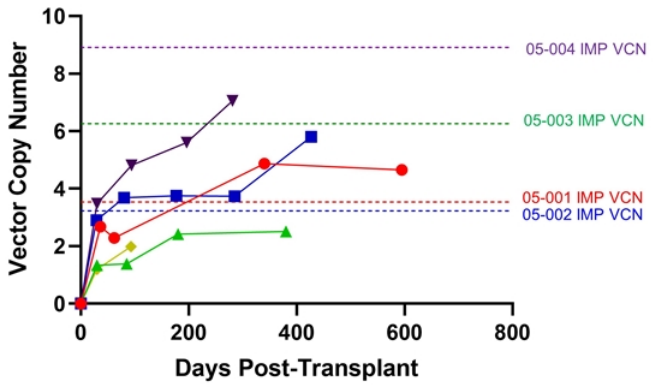
Engraftment was rapid:

- 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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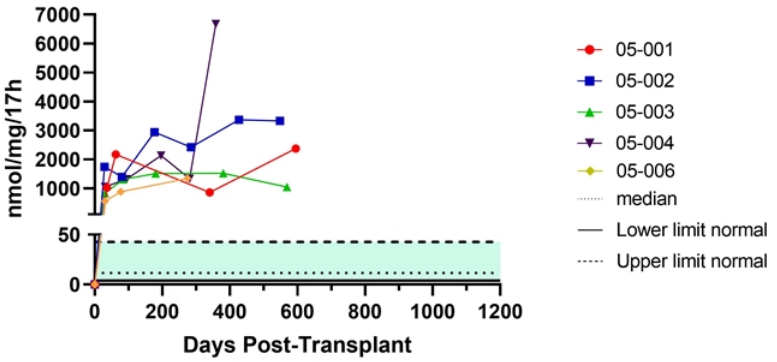
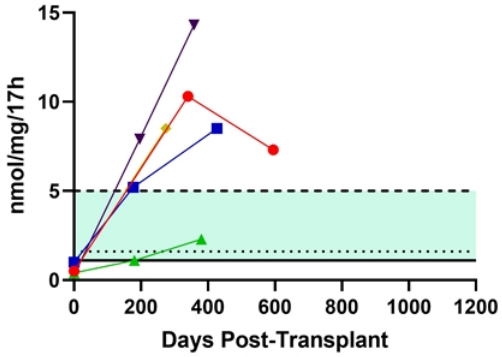
SGSH Enzyme Activity – Increase in CNS and periphery

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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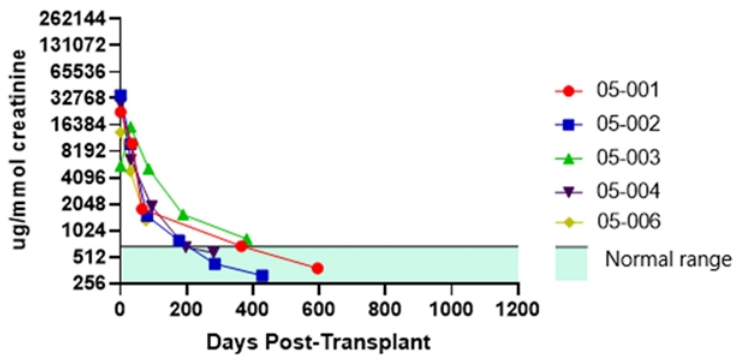
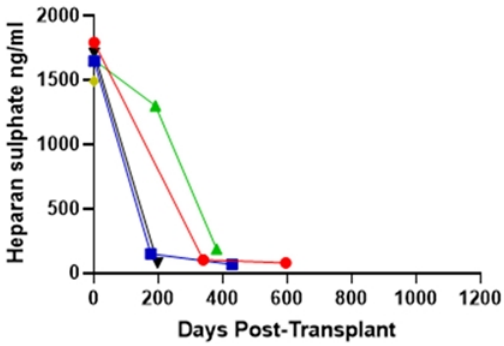
Heparan Sulfate Levels – Reduction in CNS and periphery

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

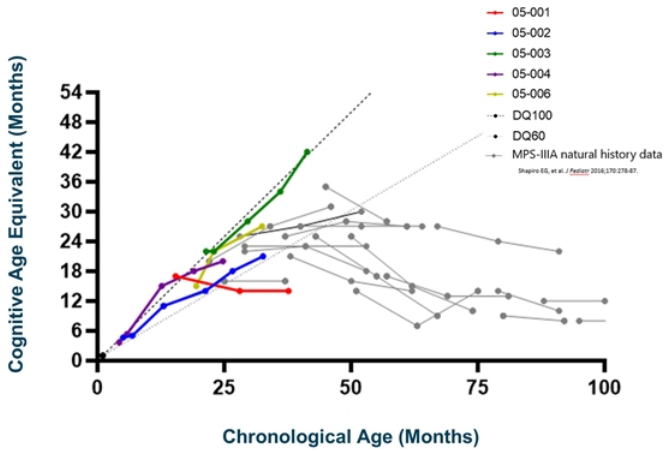
Dr. Simon Jones

Orchard therapeutics

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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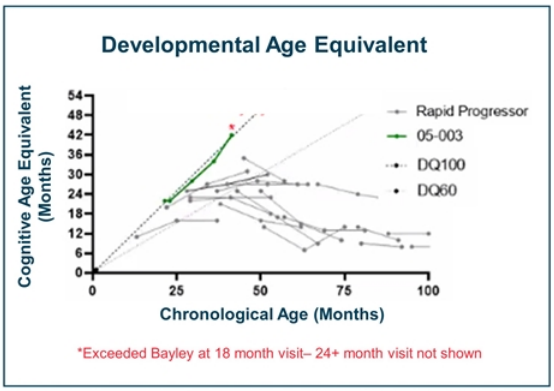
Patient 003 Summary

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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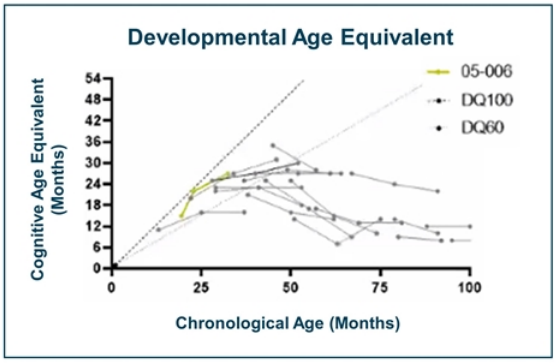
Patient 006 Summary

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

Back-up Appendix

ASH IR Event Agenda

AGENDA TOPIC	SPEAKER	
Orchard's HSC Gene Therapy and MPS-IIIA Disease Overview	Bobby Gaspar	
OTL-201 Data Update	Prof Rob Wynn	
Q&A	Leslie Meltzer	

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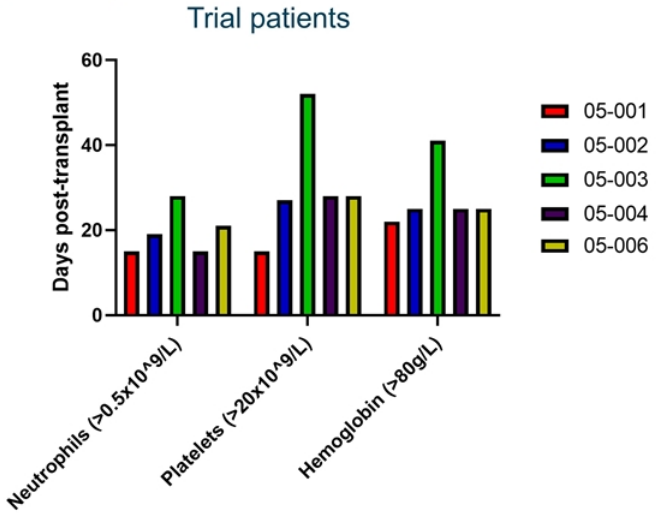
Engraftment

- 4 days of MAC busulfan conditioning (8 doses) and 2 days rest prior to IMP infusion
- Red cell and platelet transfusions, G-CSF routinely, nutritional support and analgesia as supportive therapy through transplant



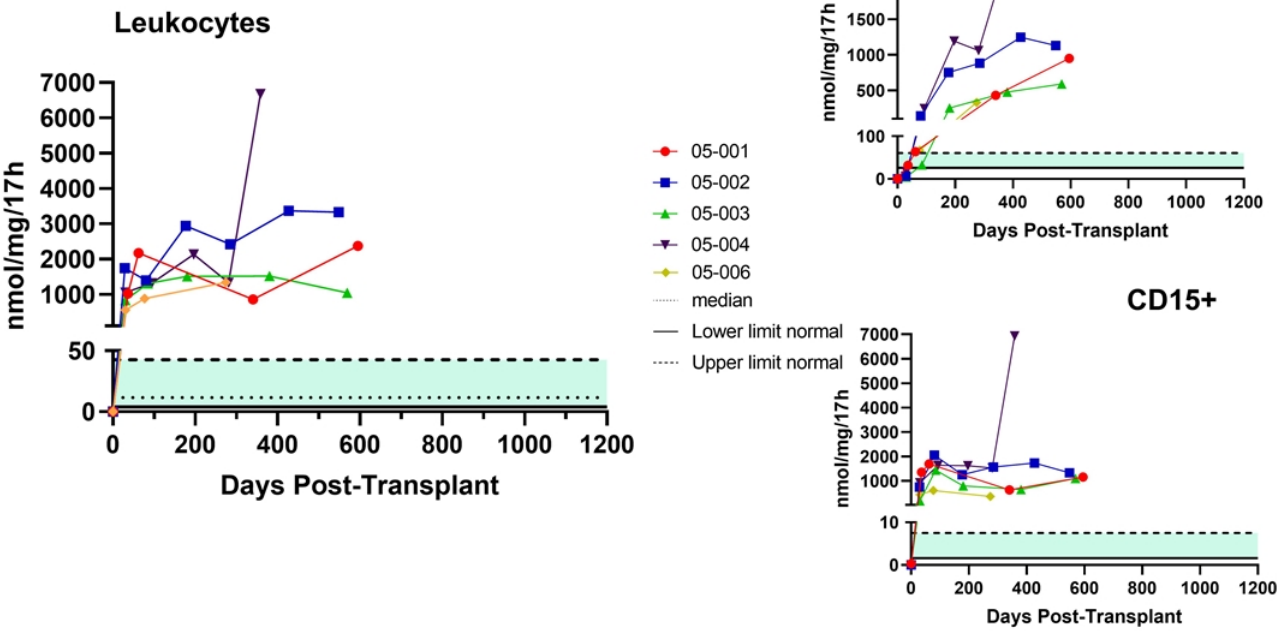
- Engraftment achieved in all patients
- Mild VOD in patient 05-002
- Delayed (over 42 days) engraftment in patient 05-003 (Likely due to primary CMV viraemia around the time of transplant)

SAEs

SAE	Patient	Description
1	05-002	Fever, grade 2, infection following line insertion prior to conditioning
2	05-002	Sinusoidal obstructive disease (Veno-occlusive disease (VOD)) related to conditioning (busulfan)
3	05-002	Subdural haematoma. Not considered related to the IMP. Possibly related to low platelets from VOD or underlying MPSIIIA disease
4	05-003	Fever, grade 1, related to leukapheresis
5	05-003	Delayed engraftment (post 42 days). Clear engraftment of Neutrophils (+day 28) and reticulocytes (+day 41) but platelets remained out of normal range until day 52 Likely due to primary CMV viraemia around the time of transplant
6	05-001	Excessive sedation following general anaesthetic (sleepiness)

There have been no deaths or evidence of insertional oncogenesis or clonal expansion.

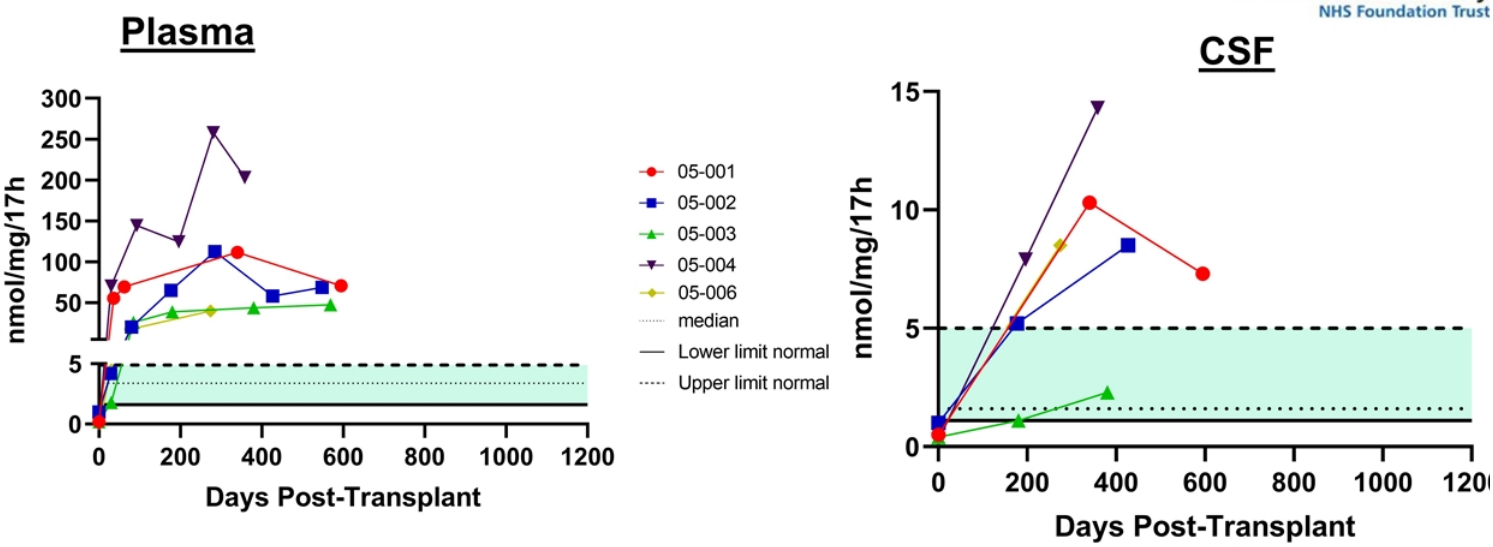
SGSH Activity Levels



- **Peripheral SGSH enzyme data shows supraphysiological SGSH levels**

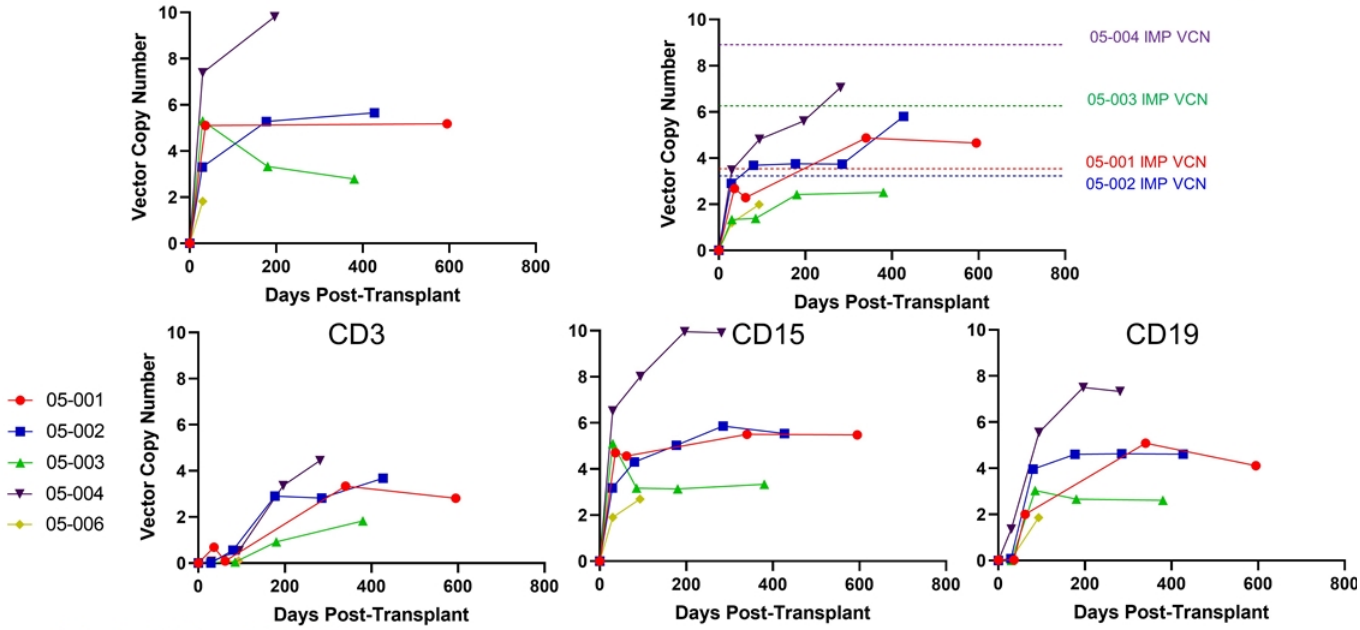
SGSH activity levels

Manchester University NHS Foundation Trust



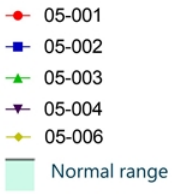
- CSF SGSH is within or above normal range at 6 months and at last follow-up

Vector Copy Number



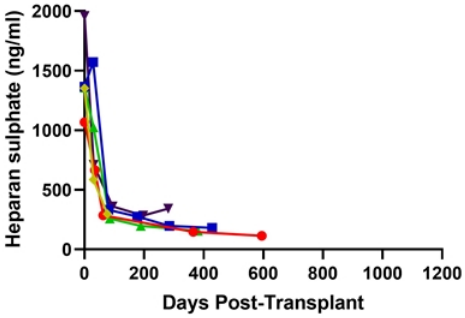
- VCN consistent with input in IMP
- VCN measurable rapidly in CD15+ cells, slower in CD19+ and later in CD3+ lineages
- In all patients, there is no evidence of clonal expansion

Heparan sulphate storage

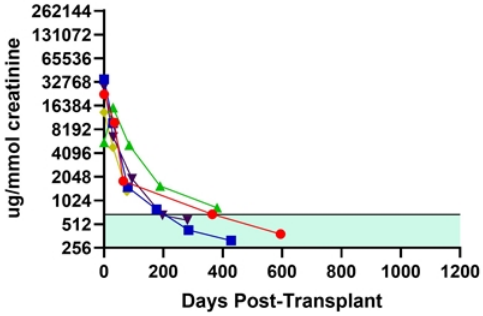


Manchester University NHS Foundation Trust

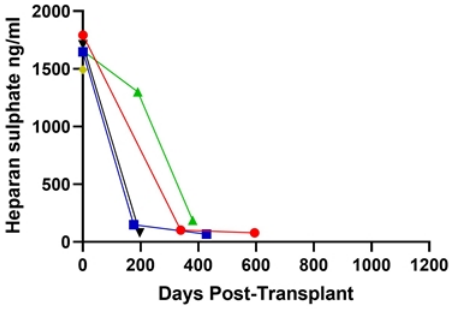
Plasma HS



Urine HS



CSF HS



- **Rapid HS reductions in plasma (>82%) and urine (>90%)**
- **Reduction in CSF HS – never achieved with allogeneic bone marrow transplant**

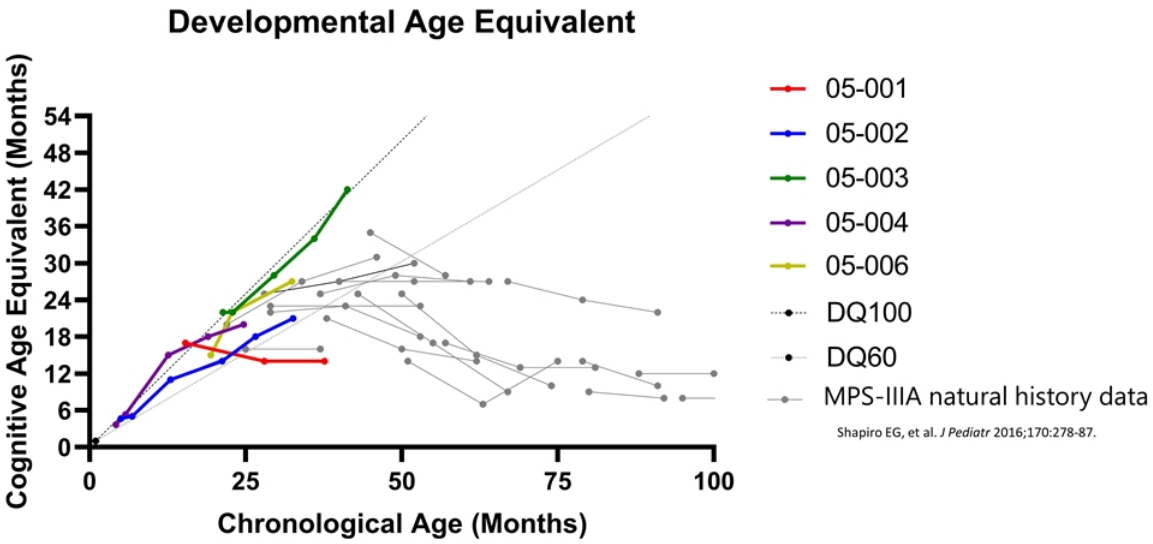
Neurocognitive outcomes, SUMMARY

- Change in **cognitive function (age equivalent scores)** against natural history of MPSIIIA
- Change in patient behaviour, patient QoL and daily living – data not formally presented, important to patients and to regulators

➢ Specials patient had suggested an attenuated phenotype compared to natural history, no loss of skills

➢ Early follow up in trial patients
  - ➢ 4 out of 5 patients actively gaining skills in the normal range
  - ➢ Developmental progression not seen in MPSIIIA, acquisition of speech, continence and complex play requiring concentration, engaged, wearing glasses and a mask
  - ➢ Longer follow up needed to assess outcomes, and ongoing

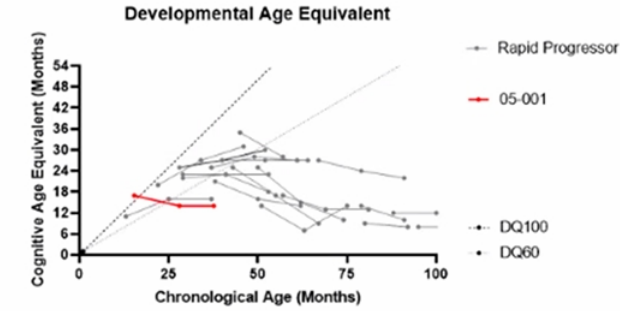
Patient 006

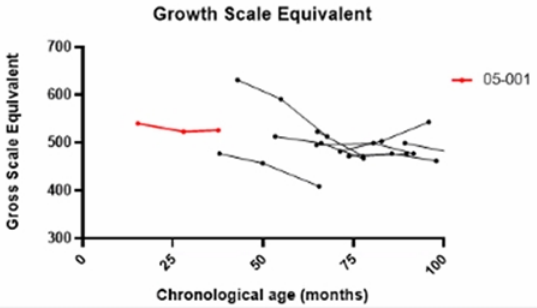

Developmental Age Equivalent
Cognitive Age Equivalent (Months)
54
48
42
36
30
24
18
12
6
0
0
25
50
75
100
Chronological Age (Months)
05-001
05-002
05-003
05-004
05-006
DQ100
DQ60
MPS-IIIA natural history data
Shapiro EG, et al. *J Pediatr* 2016;170:278-87.

Patient 05-001 Summary:

Patient	Gender	Age at treatment	Screening DQ
05-001	Female	18.3 months	110

- Australian patient, affected older sibling
- ADD NATIVE LANGUAGE
- Covid restrictions have hampered number of visits possible
- In last assessment at 18 months has:
  - struggled with tasks involving reciprocity and copying
  - able to continue to perform tasks which could be approached intuitively
  - Limited attention span
- Hearing deficit present which likely affect quality of interactions

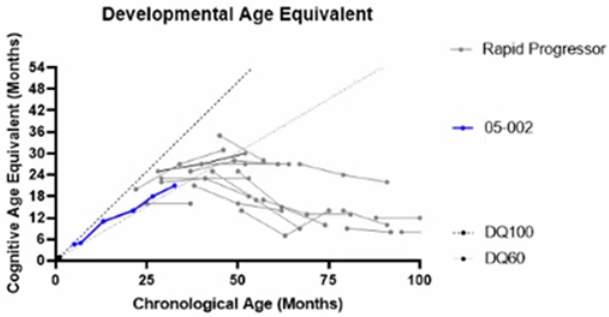


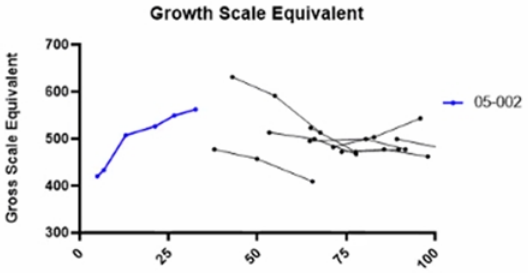


Patient 05-002 Summary:

Patient	Gender	Age at treatment	Screening DQ
05-002	Male	8.6 months	95

- German speaking, older sibling (deceased) with MPSIIIA, unaffected twin
- 24 months post-transplant (~33 months)
- Most recent assessment showed change in engagement and reciprocity
- Clear evidence of desire to please and participate
- Continuing refinements in motor performance
- Parents feel he continues to develop in a consistent fashion to unaffected twin sibling
- Shy to start, but has warmed up
- Good evidence of imaginative and caring play with toys
- Following (low side) average trajectory

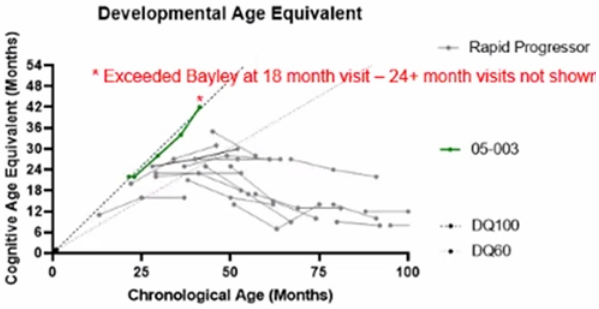


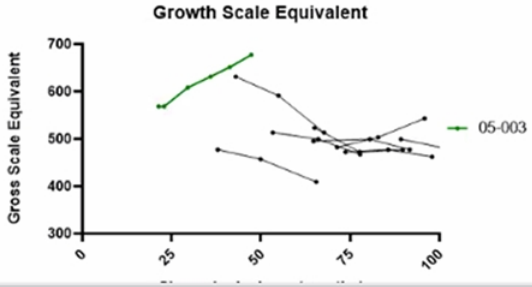


Patient 05-003 Summary:

Patient	Gender	Age at treatment	Screening DQ
05-003	Female	23.3 months	105

- German speaking, no family history
- Seen at 24 months post-transplant last week
  - Above Bayley scale AE>42 months in all areas
  - Transitioned to age appropriate assessment (Kaufman - 3 out of 4 assessments were comfortably in the average range)
  - Engaged well, good eye contact
  - Many examples of typical age appropriate development e.g. Went to the toilet unassisted and clearly told father "I can do it on my own and will call you if I need you". Was clearly delighted to tell us that she had done a "ka ka" and in a 4 year old style thought this was very funny. Reminded dad before going for lunch "hast du Geld?" (Do you have money?)
  - Enjoyed activities, smiled and laughed
  - Tried to engage unfamiliar adults in play
  - 6+ word german sentence, variety of stuctures
  - Spontaneously counted (Drei kuken (3 chicks), zwei hunde (two dogs)), colour knowledge and naming whilst being read to
  - Counted easily to 15
  - Knows age, full name, where she lives, able to retell an event from Preschool
  - Fantastic motor development – runs, balances and jumps (two footed!) well





Patient 05-003 Summary:

Patient	Gender	Age at treatment	Screening DQ
05-003	Female	23.3 months	105

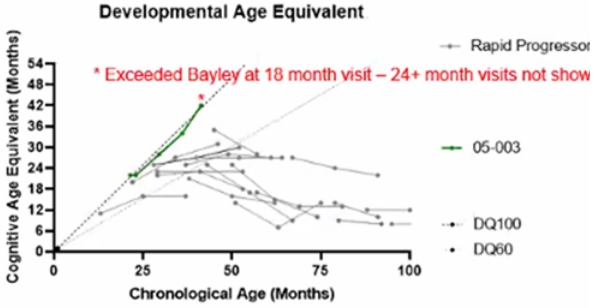
MPSIIIA children never reach the Kaufman!!

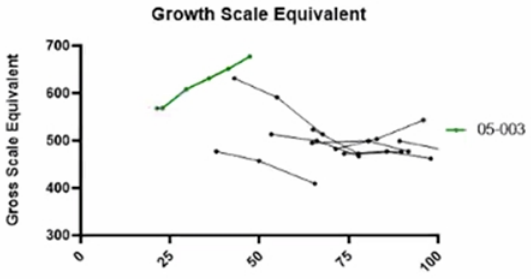
Kaufman -II Assessment:
Attempted for first time
Engaged well but tired towards the end.

- NVI Standard Score: 87 (95% CI 80-96)
- Conceptual thinking Scaled Score 9 (centile 37)
- Face Recognition Scaled Score 5 (centile 5) *we feel like she just did not like/ understand this task
- Triangles Scaled Score 9 (centile 37)
- Hand Movements Scaled Score 9 (centile 37)

3 out of 4 assessments were comfortably in the Average Range.

Not appropriate to plot on same scale as Bayley

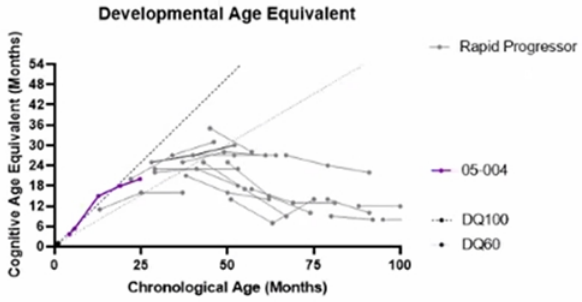


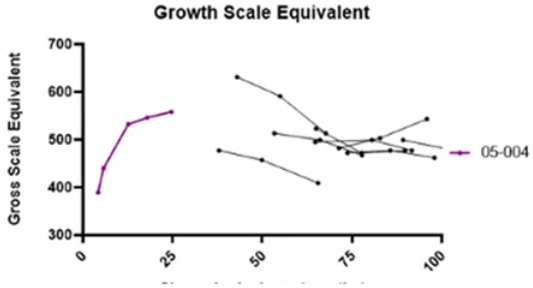


Patient 05-004 Summary:

Patient	Gender	Age at treatment	Screening DQ
05-004	Male	6.2 months	85

- German speaking, older sibling (deceased) with MPSIIIA
- 18 months post-transplant (~2 years)
- Most recent assessment showed:
  - some nice turn taking interactions
  - very interested in drawing
  - Change in reciprocity since previous assessment much more engageable
  - Motor refinements and enjoyed running and kicking the football





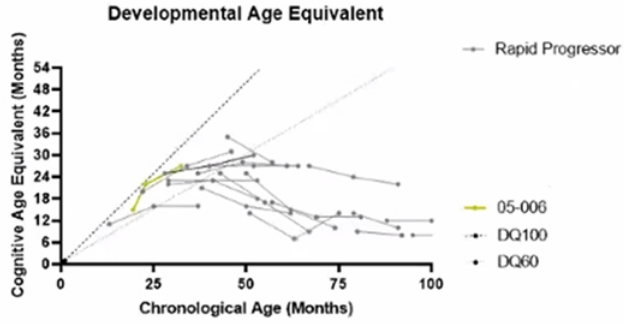
Patient 05-006 Summary:

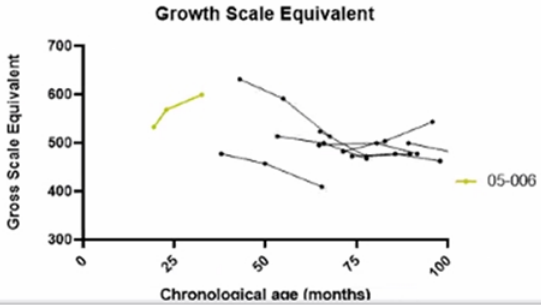
Patient	Gender	Age at treatment	Screening DQ
05-006	Male	23.6 months	85

- Hong Kong national, speaks Cantonese, older affected sibling
- Last seen in person at 9 months post-transplant (as early 12 month visit)
- Recent 12 month video call with family and translator to complete the Vineland assessment
- Great evidence of reciprocity
- Over video, said hello and engaged through the camera
- Engages in imaginative play with dinosaurs/animals
- Language developing not regressing
- Fantastic eye contact and attention

Parental narrative:

"*After receiving treatment, Lucas obviously has higher learning and social skills than his brother of the same age. Lucas started kindergarten in early September this year. He quickly adapted to campus life and liked to imitate others. Hope to see more progress from him in the future.*"





Orchard Therapeutics Announces Promising Early Neurocognitive Outcomes from Ongoing Proof-of-concept Study of OTL-201 in MPS-IIIA

All patients achieved sustained engraftment and supraphysiological SGSH enzyme levels with median 1.5 years follow-up

Four out of five patients demonstrated gain of cognitive skills in line with development in healthy children with one patient showing a marked improvement compared to disease natural history

Treatment with OTL-201 was generally well-tolerated

Company to host conference call and webcast at 5:00 p.m. EST

BOSTON and LONDON, December 12, 2022, (GLOBE NEWSWIRE) — Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced early clinical findings, including the first neurocognitive results, from its ongoing proof-of-concept (PoC) study of OTL-201, an investigational hematopoietic stem cell (HSC) gene therapy being developed for the treatment of mucopolysaccharidosis type IIIA (MPS-IIIA), also known as Sanfilippo syndrome type A. The data are being featured as part of an oral presentation at the ongoing 64th American Society of Hematology (ASH) Annual Meeting & Exposition in New Orleans.

“These are encouraging results for children living with MPS-IIIA and their families, who currently have no effective treatment options,” said Professor Robert Wynn, chief investigator at The Royal Manchester Children’s Hospital, part of Manchester University NHS Foundation Trust (MFT). “In addition to sustained engraftment of gene-corrected cells and supraphysiological SGSH enzyme levels in the periphery, the early neurocognitive findings show most patients are gaining skills in line with the development of healthy children. In one patient, we also have seen a marked improvement from disease natural history, and we hope to see similar results in the other patients with longer follow-up.”

The oral presentation at ASH 2022 will showcase the first neurocognitive data for all five patients enrolled in the trial and extend upon previously presented biochemical results. Trial patients were 6 to 24 months of age at the time of administration of OTL-201, and the preliminary results are based on a median follow-up of 1.5 years (range: 9-24 months).

Specifically, the biochemical results show the following in all patients:

- Engraftment is sustained to date, with supraphysiological levels of N-sulphoglucosamine sulphohydrolase (SGSH) enzyme measurable in leukocytes 38- to 91-fold above median normal range at one-month post-treatment.
- Supraphysiological SGSH levels were also rapidly detected in $CD15^+$ cells, $CD3^+$ cells, and plasma and have been maintained through the last follow-up visit for each patient. SGSH levels in cerebrospinal fluid (CSF) were within or above normal range by 6-months post-treatment and at the most recent follow-up.
- Abnormal heparan sulfate levels at baseline were rapidly reduced post-treatment in urine (>90 percent), plasma (>82 percent), as well as CSF, and has continued to be maintained at these levels in all evaluated patients.

Early neurocognitive outcomes also indicate that:

- Since receiving the investigational gene therapy, four out of five patients showed gain of cognitive skills in line with development in healthy children compared to natural history of MPS-IIIA.[i]
    - A marked improvement compared with natural history of the disease was observed in one patient at 18 months of follow up.
    - Three additional patients are currently within the normal development quotient (DQ) range at 9 to 18 months post-treatment but require longer follow-up to assess outcomes.
    - Gain of cognitive skills is assessed in this study through evidence of speech acquisition, continence and complex play requiring concentration.

Treatment with OTL-201 was generally well-tolerated in the initial study population. Of the six serious adverse events (SAEs) reported to date, four were thought to be due to conditioning or leukapheresis and one was related to background disease. One patient had delayed platelet engraftment until day 52 post-treatment likely due to Cytomegalovirus infection around the time of infusion. The lentiviral vector integration profile was consistent with other lentiviral-based HSC gene therapy studies and there has been no indication of insertional oncogenesis and no evidence of clonal dominance due to integration into oncogenes in samples analyzed to date.

“These promising findings continue to demonstrate the ability of our HSC gene therapy platform to enable the migration of gene-corrected cells into the central nervous system and the localized delivery of therapeutic enzymes and proteins to the brain to potentially correct neurodegeneration in multiple severe conditions, building on our programs in metachromatic leukodystrophy and MPS-IH,” said Leslie Meltzer, Ph.D., chief medical officer of Orchard Therapeutics. “While these early results are encouraging, longer follow up is needed as the majority of the patients in this trial have not reached the age where the most severe stages of disease progression typically manifest. We are working with our collaborators at The University of Manchester and Royal Manchester Children’s Hospital to continue following patients in this ongoing study and more fully characterize the clinical profile of OTL-201.”

Five patients aged 6 to 24 months, with a rapidly progressive MPS-IIIA phenotype confirmed by an independent metabolic disease expert, were administered investigational OTL-201 as part of this ongoing PoC trial, sponsored by The University of Manchester (UoM), conducted at Royal Manchester Children’s Hospital, and funded by Orchard Therapeutics. Primary study objectives include safety, tolerability and peripheral expression of SGSH in total leukocytes at 12 months. Secondary study objectives include overall survival and neurocognition as measured by the Bayley Scales of Infant and Toddler Development (BSID-III) or the Kaufman Assessment Battery for Children (KABC-II). The OTL-201 program and this investigator-led clinical trial follow over a decade of development and pre-clinical work by Brian Bigger, Ph.D., professor of cell and gene therapy at UoM.

Patients enrolled in the ongoing PoC trial will be followed for a minimum of three years during which time the study investigators will continue to report additional biochemical and clinical outcomes. The OTL-201 program in MPS-IIIA presents multiple development and commercial synergies with Orchard’s other neurometabolic programs, and the condition represents a significant medical need given there are no approved therapies and treatment with allogeneic HSC transplant has not been shown to be effective for MPS-IIIA patients.

Conference Call and Webcast

A live webcast will be available under “News & Events” in the Investors & Media section of the company’s website at www.orchard-tx.com. A replay of the webcast will be archived on the Orchard website following the presentation.

About MPS-IIIA

Mucopolysaccharidosis type IIIA (MPS-IIIA), also known as Sanfilippo syndrome type A is a rare and life-threatening metabolic disease. People with MPS-IIIA are born with a mutation in the *N-sulphoglucosamine sulphohydrolase (SGSH)* gene which, when healthy, helps the body break down sugar molecules called mucopolysaccharides. The buildup of mucopolysaccharides in the brain and other tissues leads to intellectual disability and loss of motor function. MPS-IIIA occurs in approximately one in every 100,000 live births. Life expectancy of children born with MPS-IIIA is estimated to be between 10-25 years.

About OTL-201

OTL-201 is an investigational hematopoietic stem cell gene therapy being developed for the treatment of MPS-IIIA. It uses a lentiviral vector to insert a functional copy of the human *SGSH* gene into a patient’s hematopoietic stem cells. OTL-201 has received rare pediatric disease designation from the U.S. Food and Drug Administration (FDA) and is currently being evaluated in an ongoing proof-of-concept clinical trial.

About Orchard Therapeutics

At Orchard Therapeutics, our vision is to end the devastation caused by genetic and other severe diseases. We aim to do this by discovering, developing and commercializing new treatments that tap into the curative potential of hematopoietic stem cell (HSC) gene therapy. In this approach, a patient's own blood stem cells are genetically modified outside of the body and then reinserted, with the goal of correcting the underlying cause of disease in a single treatment.

In 2018, the company acquired GSK's rare disease gene therapy portfolio, which originated from a pioneering collaboration between GSK and the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy. Today, Orchard is advancing a pipeline spanning pre-clinical, clinical and commercial stage HSC gene therapies designed to address serious diseases where the burden is immense for patients, families and society and current treatment options are limited or do not exist.

Orchard has its global headquarters in London and U.S. headquarters in Boston. For more information, please visit www.orchard-tx.com, and follow us on Twitter and LinkedIn.

About Manchester University NHS Foundation Trust (MFT)

Manchester University NHS Foundation Trust (MFT) is the largest NHS trust in England and a leading provider of specialist healthcare services. Its 10 hospitals are home to hundreds of world class clinicians and academic staff, committed to finding patients the best care and treatments. Its hospitals are Manchester Royal Infirmary, Saint Mary's Hospital, Royal Manchester Children's Hospital, Manchester Royal Eye Hospital, North Manchester General Hospital, University Dental Hospital of Manchester, Trafford General Hospital, Altrincham Hospital, Wythenshawe Hospital and Withington Hospital. More information is available at: www.mft.nhs.uk.

About The University of Manchester

The University of Manchester is a member of the prestigious Russell Group and one of the UK's largest single-site universities. We have over 40,000 students, 12,000 staff and, with almost 480,000 former students from more than 190 countries, are home to the largest alumni community of any campus-based university in the UK. We are ranked in the top ten of the Times Higher Education (THE) Impact Rankings globally; are the top UK University for graduate employability according to The Graduate Market in 2022 and no fewer than 25 Nobel laureates have either worked or studied here. Visit www.manchester.ac.uk for further information or https://www.manchester.ac.uk/discover/vision/ for our latest strategic vision.

Availability of Other Information About Orchard

Investors and others should note that Orchard communicates with its investors and the public using the company website (www.orchard-tx.com), the investor relations website (ir.orchard-tx.com), and on social media (Twitter and LinkedIn), including but not limited to investor presentations and investor fact sheets, U.S. Securities and Exchange Commission filings, press releases, public conference calls and webcasts. The information that Orchard posts on these channels and websites could be deemed to be material information. As a result, Orchard encourages investors, the media, and others interested in Orchard to review the information that is posted on these channels, including the investor relations website, on a regular basis. This list of channels may be updated from time to time on Orchard's investor relations website and may include additional social media channels. The contents of Orchard's website or these channels, or any other website that may be accessed from its website or these channels, shall not be deemed incorporated by reference in any filing under the Securities Act of 1933.

Forward-looking Statements

This press release contains forward-looking statements, which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Forward-looking statements include express or implied statements relating to, among other things, Orchard's business and product development strategy and goals, including the therapeutic potential of OTL-201, Orchard's expectations with respect to regulatory submissions for its product candidates, including OTL-201, and Orchard's expectations regarding its ongoing preclinical and clinical trials, including the timing of enrollment for clinical trials and release of additional preclinical and clinical data, and the likelihood that data from clinical trials will be positive and support further clinical development and regulatory approval of Orchard's product candidates. These statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, many of which are beyond Orchard's control, which could cause actual results to differ materially from those contemplated in these forward-looking statements. In particular, these risks and uncertainties include, without limitation: the risk that prior results, such as signals of safety, activity or durability of effect, observed from clinical trials of OTL-201 will not continue or be repeated in Orchard's ongoing or planned clinical trials of OTL-201, will be insufficient to support regulatory submissions or support or maintain marketing approval in the US or European Union, or that long-term adverse safety findings may be discovered; and the risk that any one or more of Orchard's product candidates, including the OTL-201, will not be approved, successfully developed or commercialized. Given these uncertainties, the reader is advised not to place any undue reliance on such forward-looking statements.

Other risks and uncertainties faced by Orchard include those identified under the heading "Risk Factors" in Orchard's most recent annual or quarterly report filed with the U.S. Securities and Exchange Commission (SEC), as well as subsequent filings and reports filed with the SEC. The forward-looking statements contained in this press release reflect Orchard's views as of the date hereof, and Orchard does not assume and specifically disclaims any 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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i *Cognitive function measured via standard scores, age-equivalent scores, development quotient (DQ) and gross scale equivalent [BSID-III] or [KABC-II]*

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