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): **May 18, 2023**

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 May 23, 2023, Orchard Therapeutics plc (the "Company") intends to hold a conference call and webcast to review data presented at the 26th Annual Meeting of the American Society of Gene and Cell Therapy in Los Angeles, California. A copy of the Company's presentation is being furnished as Exhibit 99.1 to this Current Report on Form 8-K (this "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 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 or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events.

On May 18, 2023, the Company issued a press release titled "Orchard Therapeutics Presents Data from Research Programs at ASGCT Demonstrating the Ability of HSC Gene Therapy to Address Larger Indications." A copy of the press release is attached as Exhibit 99.2 to this Report and is incorporated herein by reference.

On May 19, 2023, the Company issued a press release titled "Orchard Therapeutics Announces Positive Clinical and Preclinical Data in Programs Targeting Neurometabolic and CNS Disorders at ASGCT." A copy of the press release is attached as Exhibit 99.3 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 May 18, 2023
99.3	Press release, dated May 19, 2023
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: May 23, 2023

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

Exhibit 99.1

ASGCT Data Review

IR webcast
May 23, 2023

ASGCT IR Event Agenda


TIME	AGENDA TOPIC	SPEAKERS
8:00 – 8:10 a.m.	**Orchard's HSC Gene Therapy Platform and ASGCT Overview**	Bobby Gaspar CEO
8:10 – 8:30 a.m.	**Clinical Data: OTL-203 (MPS-IH) + OTL-201 (MPS-IIIA)**	Leslie Meltzer CMO
8:30 – 8:40 a.m.	**Preclinical: OTL-204 (GRN-FTD) + OTL-104 (NOD2-CD)**	Bobby Gaspar CEO
8:40 – 9:00 a.m.	**Q&A**	

Orchard therapeutics

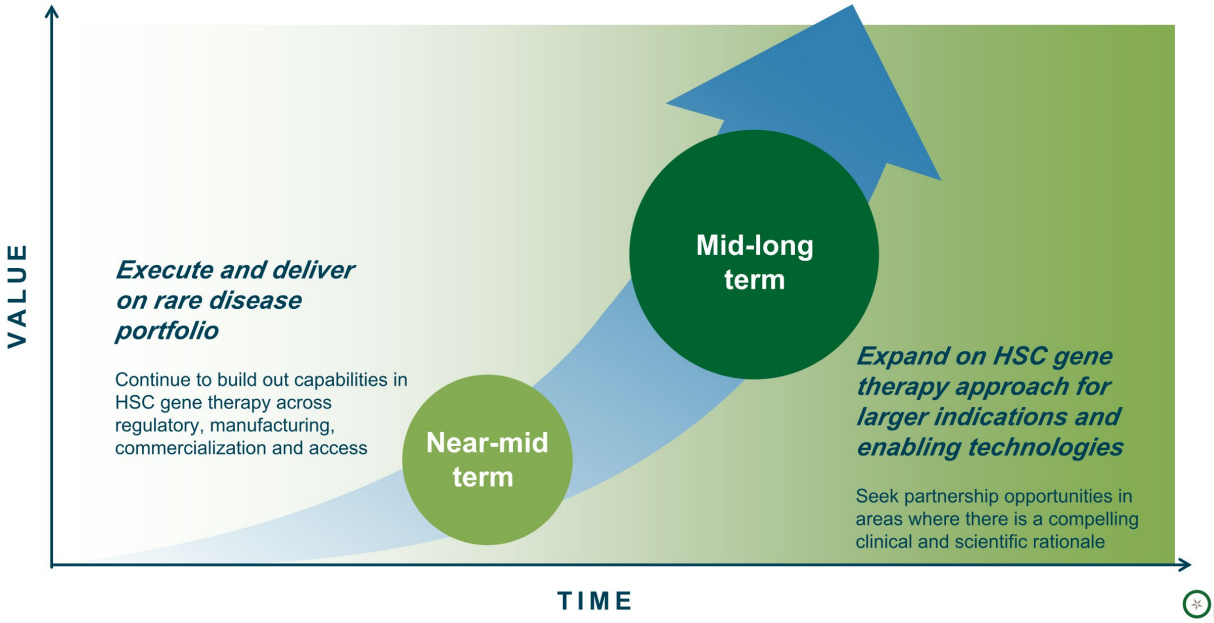
Forward-looking Statements

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

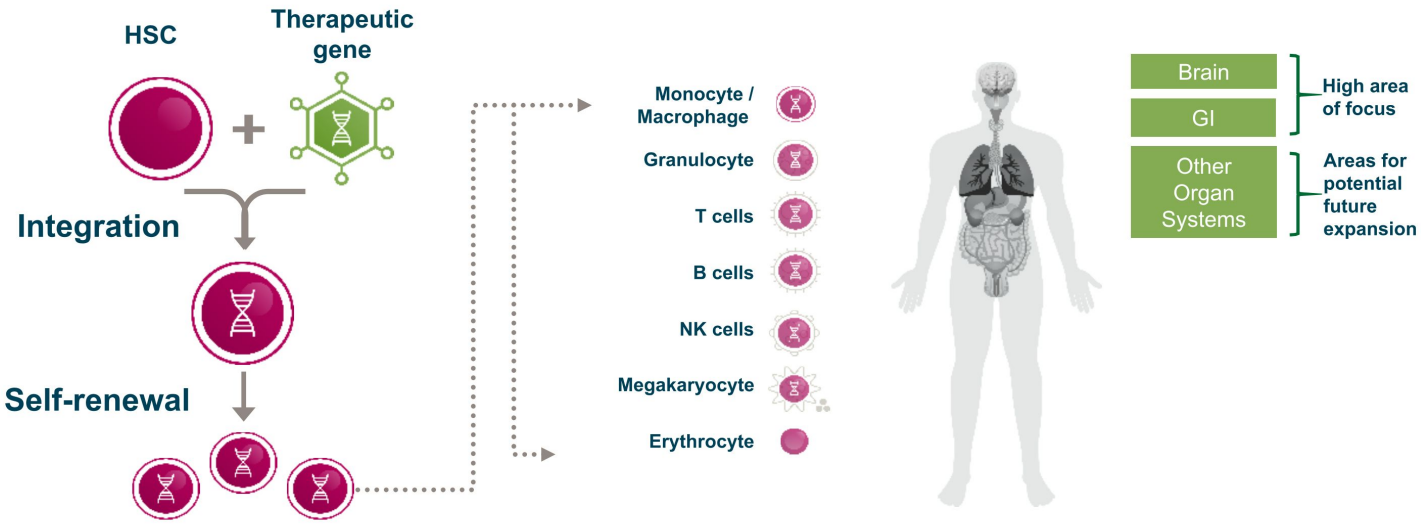
Orchard's Vision to End the Devastation Caused by Severe and other Genetic Diseases



HSC= hematopoietic stem cell

Orchard therapeutics

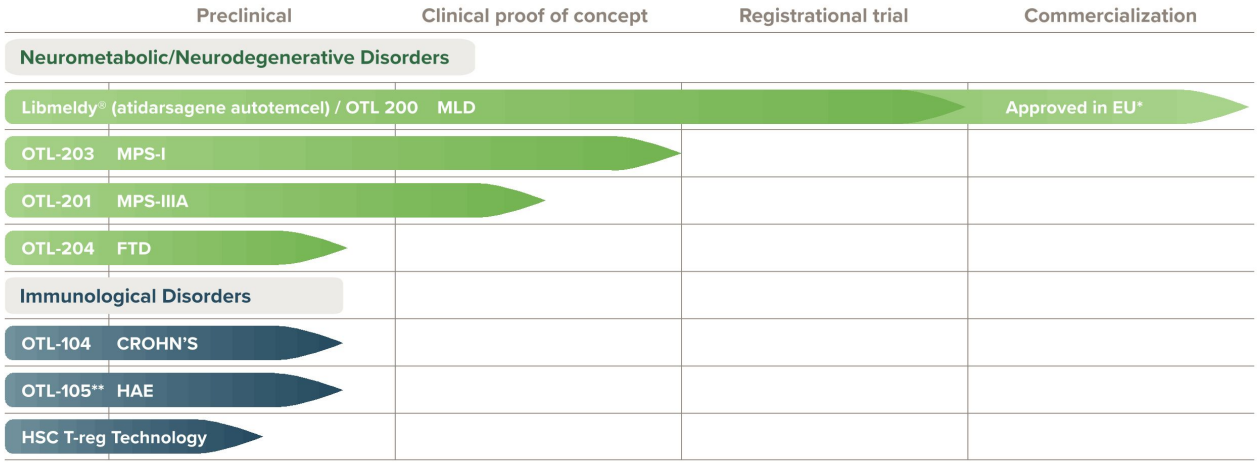
HSC Gene Therapy Offers a Highly Differentiated Approach



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

Orchard therapeutics

Validated Rare Disease Pipeline with Opportunities for Expansion



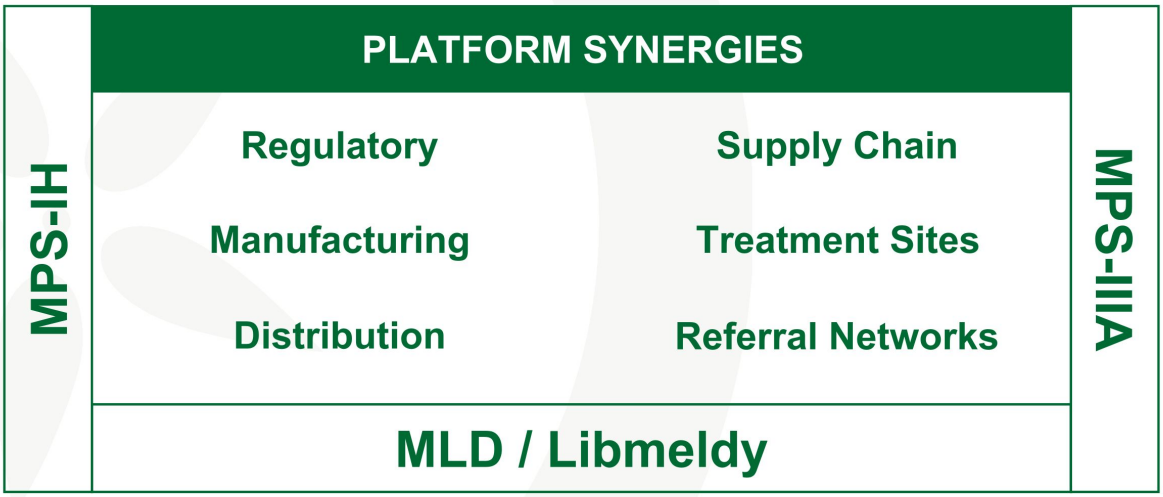
Several additional research and preclinical programs under development.

*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.

**OTL-105 partnered with Pharming Group N.V.

Orchard therapeutics

Significant Platform Synergies That Can be Leveraged Across Neurometabolic Pipeline



Orchard therapeutics

ASGCT Snapshot: Six presentations and three oral presentations across five programs

- **OTL-203 for MPS-IH: New PoC data shows extensive metabolic correction in the skeletal system, including normal growth rates, improvement in joint function and progressive acquisition of motor skills**
- **OTL-201 for MPS-IIIA: Updated data from ongoing PoC study show additional favorable neurocognitive outcomes compared to disease natural history with median follow-up out to 2.5 years**
- **OTL-204 for GRN-FTD: First preclinical data highlighting ability of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers**
- **OTL-104 for NOD2-CD: Preclinical proof-of-concept data show the therapeutic potential in a severe and treatment-refractory form of the disease**

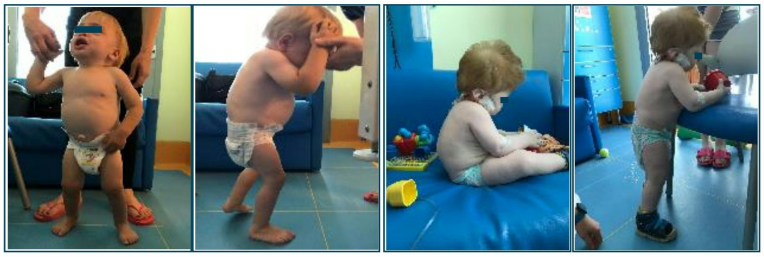
ASGCT IR Event Agenda

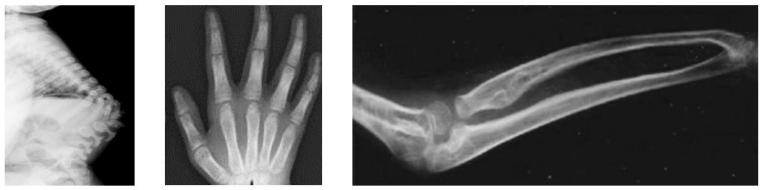
TIME	AGENDA TOPIC	SPEAKERS
8:00 – 8:10 a.m.	**Orchard's HSC Gene Therapy Platform and ASGCT Overview**	Bobby Gaspar CEO
8:10 – 8:30 a.m.	**Clinical Data: OTL-203 (MPS-IH) + OTL-201 (MPS-IIIA)**	Leslie Meltzer CMO
8:30 – 8:45 a.m.	**Preclinical: OTL-204 (GRN-FTD) + OTL-104 (NOD2-CD)**	Bobby Gaspar CEO
8:45 – 9:00 a.m.	**Q&A**	

New OTL-203 Data in MPS-IH

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

- Deficiency of **IDUA enzyme** leads to accumulation of heparan and dermatan sulfate
- **Multisystemic** neurometabolic condition affecting cognition, **growth and skeletal** function
- **Current standard of care: HSCT** and/or ERT as a bridging or chronic therapy but with **significant limitations**
- **Incidence:** ~1 in 100,000 live births; Hurler syndrome accounts for 60%[1]
- **NBS established** in some geographies, including[1]
  - National: Netherlands, Taiwan, Austria*
  - Regional/Provincial: Italy, Canada
  - U.S: 33 states screening as of May 2023





MPS Symposium July 2021; Moore 2008; mps1disease.com

* private paid program (Archimed)

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

OTL-203 (MPS-IH): Interim Proof-of-Concept (PoC) Study Results Published in NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 18, 2021 VOL. 385 NO. 21

Hematopoietic Stem- and Progenitor-Cell Gene Therapy for Hurler Syndrome

B. Gentner, F. Tucci, S. Galimberti, F. Fumagalli, M. De Pellegrin, P. Silvani, C. Camesasca, S. Pontesilli, S. Darin, F. Ciotti, M. Sarzana, G. Consiglieri, C. Filisetti, G. Forni, L. Passerini, D. Tomasoni, D. Cesana, A. Calabria, G. Spinozzi, M.-P. Cicalese, V. Calbi, M. Migliavacca, F. Barzaghi, F. Ferrua, V. Gallo, S. Miglietta, E. Zonari, P.S. Cheruku, C. Forni, M. Facchini, A. Corti, M. Gabaldo, S. Zancan, S. Gasperini, A. Rovelli, J.-J. Boelens, S.A. Jones, R. Wynn, C. Baldoli, E. Montini, S. Gregori, F. Ciceri, M.G. Valsecchi, G. la Marca, R. Parini, L. Naldini, A. Aiuti, and M.-E. Bernardo, for the MPSI Study Group*

ABSTRACT

BACKGROUND

Allogeneic hematopoietic stem-cell transplantation is the standard of care for Hurler syndrome (mucopolysaccharidosis type I, Hurler variant [MPSIH]). However, this treatment is only partially curative and is associated with complications.

METHODS

We are conducting an ongoing study involving eight children with MPSIH. At enrollment, the children lacked a suitable allogeneic donor and had a Developmental Quotient or Intelligence Quotient score above 70 (i.e., none had moderate or severe cognitive impairment). The children received autologous hematopoietic stem and progenitor cells (HSPCs) transduced ex vivo with an α-L-iduronidase (IDUA)–encoding lentiviral vector after myeloablative conditioning. Safety and correction of blood IDUA activity up to supraphysiologic levels were the primary end points. Clearance of lysosomal storage material as well as skeletal and neurophysiological development were assessed as secondary and exploratory end points. The planned duration of the study is 5 years.

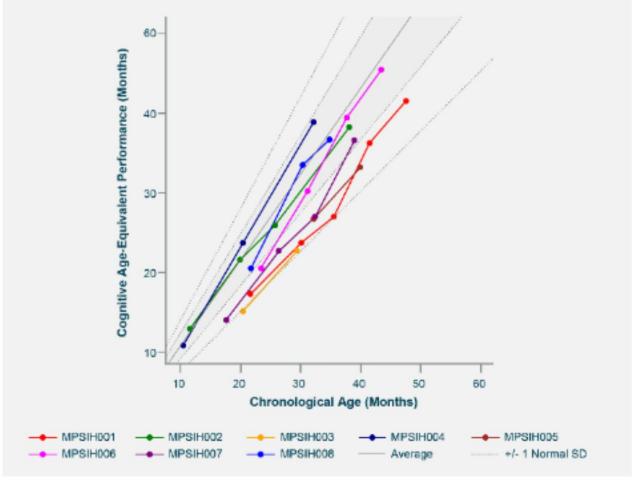
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Aiuti can be contacted at aiuti.alessandro@hsr.it or at the San Raffaele Telethon Institute for Gene Therapy, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.

*The members of the MPSI Study Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Tucci and Galimberti and Drs. Aiuti and Bernardo contributed equally to this article.

N Engl J Med 2021;385:1929-40.
DOI: 10.1056/NEJMoa2106596

Neuropsychological Tests over Time
Cognitive Age-Equivalent Score (Overall)



SD = Standard Deviation; IQ(C) = Intelligence Quotient (Cognition);
Engl J Med 2021; 385:1929-1940 DOI: 10.1056/NEJMoa2106596

Orchard therapeutics

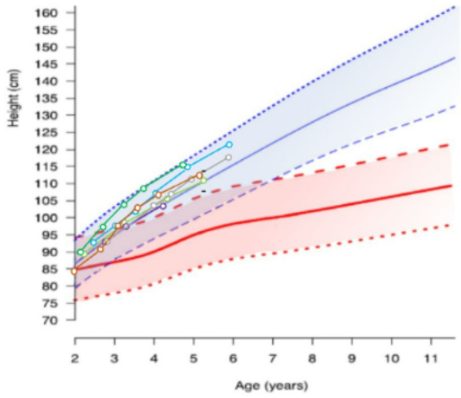
Early Skeletal Outcome After HSPC-GT for Mucopolysaccharidosis Type I Hurler

Maria Ester Bernardo, MD, PhD
"Vita-Salute San Raffaele" University Medical School
San Raffaele Telethon Institute for Gene Therapy
Milan, Italy
bernardo.mariaester@hsr.it

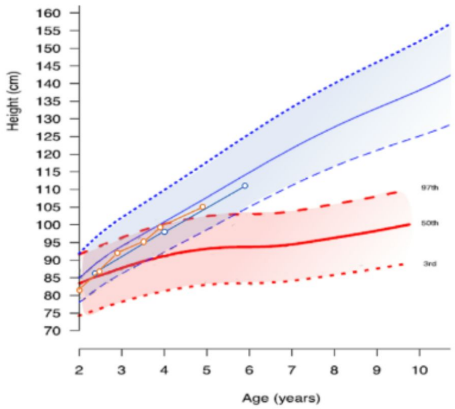
Early Clinical Skeletal Outcome: Auxological Parameters after GT

All GT pts. exhibit longitudinal growth within expected reference ranges according to age and gender, with a median height gain greater than the one observed in an external cohort of HSCT patients following a 3-year follow-up. [Short stature defined as height -2 SDS]

Growth charts males



Growth charts females



Percentiles:
WHO growth charts in blue-shadowed
MPSIH growth charts in red-shadowed

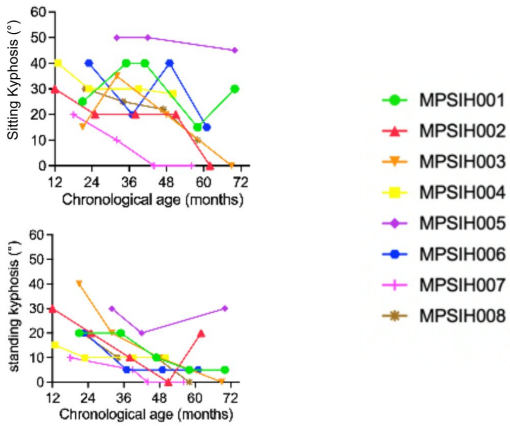
○ MPSIH001 ○ MPSIH002 ○ MPSIH004
○ MPSIH005 ○ MPSIH006 ○ MPSIH007

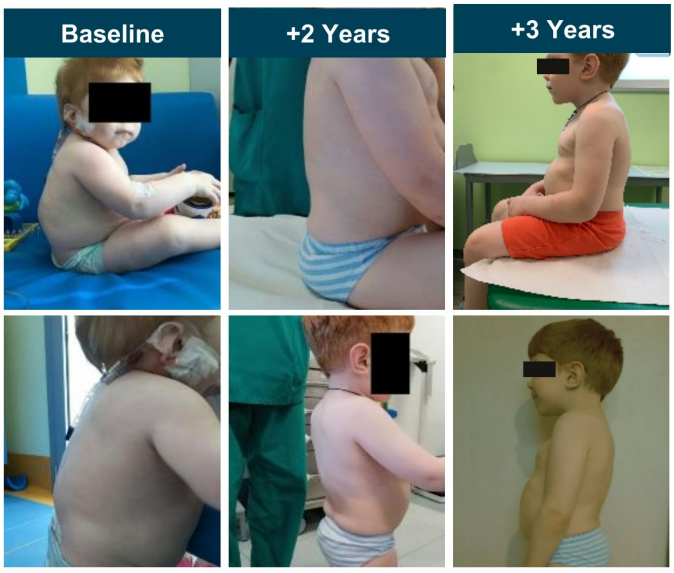
○ MPSIH003
○ MPSIH008

Orchard therapeutics

Early Clinical Skeletal Outcome: Standing & Sitting Kyphosis After GT

Clinically measurable reduction in both sitting and standing kyphosis in the majority of the pts.





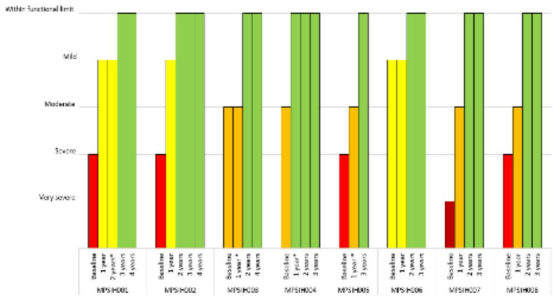
MPSIH004

Orchard therapeutics

Early Functional Skeletal Outcome

Complete and earlier normalization of joint mobility (shoulder abduction and flexion, hip and knee extension ROM) as compared with an external cohort of HSCT pts.

TMQ by Peabody scale



MPSIH004, Baseline

MPSIH004, 36 months past GT

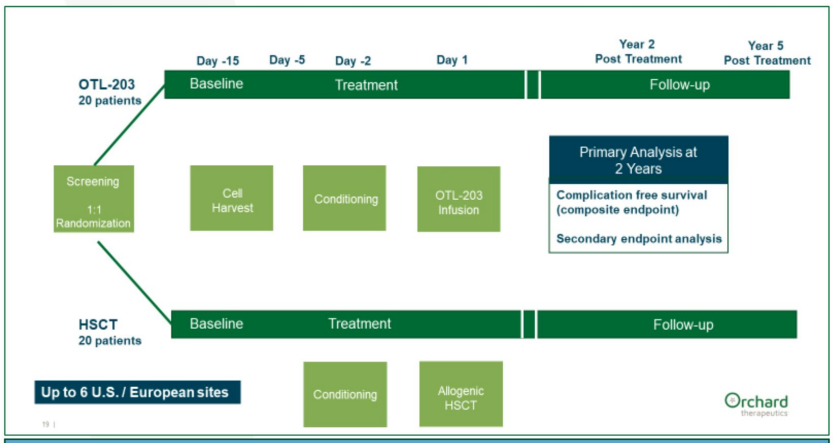
Orchard therapeutics

Data Takeaways and Next Steps

OTL-203 (MPS-IH) Moving into a Registrational Trial in 2H 2023

PoC Data Takeaways

New data shows extensive metabolic correction in the skeletal system, including normal growth rates, improvement in joint function and progressive acquisition of motor skills



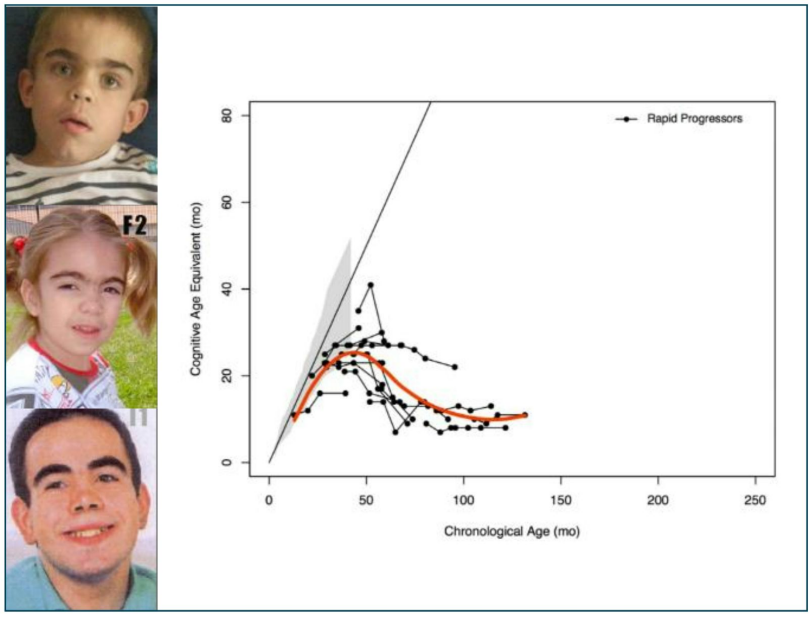
- Randomized controlled trial vs. HSCT
- 40 patients
- 2-year primary analysis
- Complication free survival composite endpoint

Orchard therapeutics

New OTL-201 Data in MPS-IIIA

MPS-IIIA is a Progressive and Devastating Disease

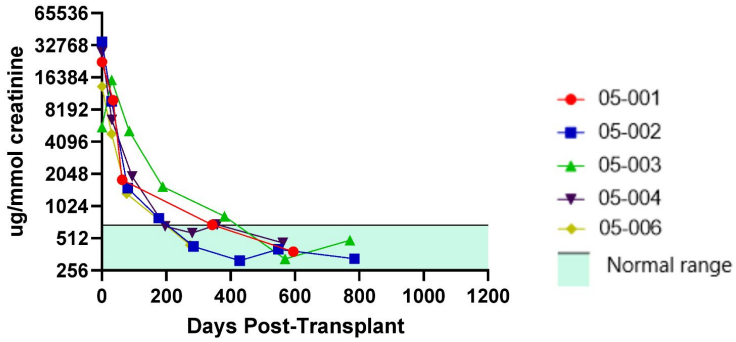
- **Sanfilippo Syndrome type A;** pathogenic variants in ***SGSH*** **gene**
- Accumulation of **substrate heparan sulfate leading to severe CNS degeneration** w/ somatic manifestations
- **Severe phenotype** – development slows from 3 years of age, followed by cognitive decline, behavioural disturbances, 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
  - Robust correction of neurocognitive decline and durability of effect *not established* for AAV approaches
- **Incidence: ~1 in 100,000 live births**



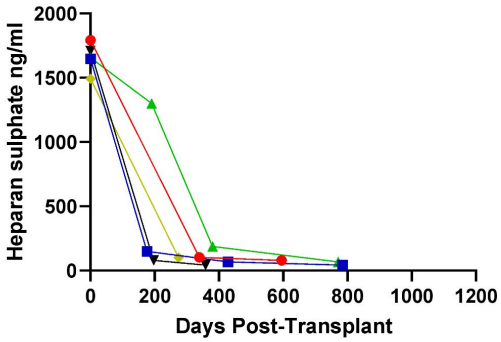
SGSH = N-Sulfoglucosamine Sulfohydrolase
Shapiro EG, et al. J Pediatr 2016;170:278-87.
Photos adapted from Natural History of Sanfilippo Syndrome in Spain; Orphanet Journal of Rare Diseases · December 2013

Heparan Sulfate Levels – Reduction in CNS and periphery

Urine HS Levels



CSF HS Levels



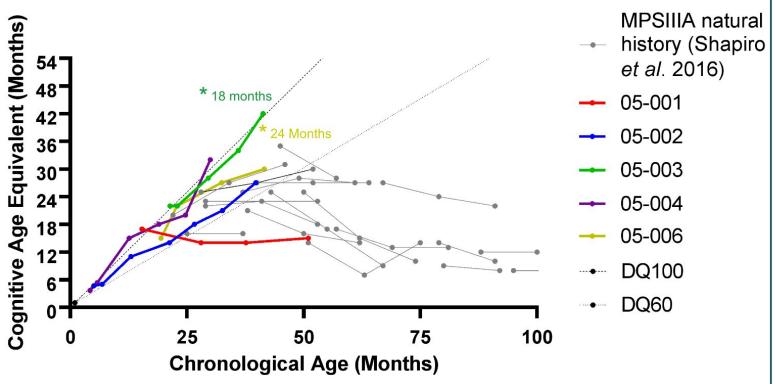
Rapid decreases from baseline of heparan sulfate in urine and CSF were seen in all evaluated patients.
Reduction in CSF HS has never been achieved with allogeneic HSCT

Orchard therapeutics

Neurocognitive Outcomes

- Patient 05-003 and 05-006 reached the ceiling of the Bayley scale (BSID-III) at 18/24 months and progressed onto the Kaufmann assessment (KABC-II) at 24/30 months
- Patient 05-003 is the first MPSIIIA patient with rapidly progressive phenotype at Manchester able to complete the Kaufman assessment
- Patient 05-003 is within normal range on Kaufmann scale at both 24- and 30-months post-transplant with gain in skills between assessments

Developmental Age Equivalent



Orchard therapeutics

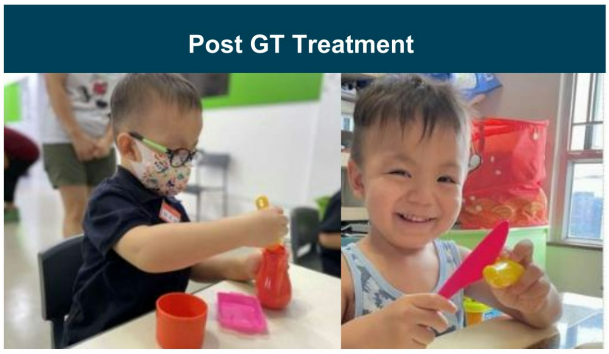
Neurocognitive Outcomes

Change **in cognitive function (age equivalent scores)** against natural history of MPSIIIA

Change in patient behavior, patient QoL and daily living

Early follow-up in trial patients

- **Gain of skills in line with development of normal children in 4 out of 5 patients**
- Developmental gains not seen in untreated MPSIIIA, e.g. acquisition of speech, continence and complex play
- Longer follow up needed to assess safety and efficacy outcomes



Orchard therapeutics

OTL-201 POC Conclusions

- ✓ **Robust, prompt, sustained, multi-lineage engraftment** of genetically modified cells
- ✓ **Supra-physiological levels** of SGSH enzyme in leukocytes and CSF and rapid and **significant reduction of substrate** observed in all compartments
- ✓ 4 / 5 patients are demonstrating **gain of cognitive skills in line with development in healthy children with two patients progressing to the Kaufman scale of cognitive assessment**

- ○ Early 2024 read-out expected – all patients will have completed 3 years of follow-up and reached at least 3 years of age

Orchard therapeutics

ASGCT IR Event Agenda

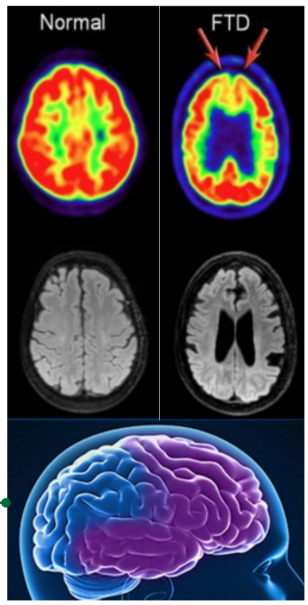
TIME	AGENDA TOPIC	SPEAKERS
8:00 – 8:10 a.m.	**Orchard's HSC Gene Therapy Platform and ASGCT Overview**	Bobby Gaspar CEO
8:10 – 8:30 a.m.	**Clinical Data: OTL-203 (MPS-IH) + OTL-201 (MPS-IIIA)**	Leslie Meltzer CMO
8:30 – 8:40 a.m.	**Preclinical: OTL-204 (GRN-FTD) + OTL-104 (NOD2-CD)**	Bobby Gaspar CEO
8:40 – 9:00 a.m.	**Q&A**	

Orchard therapeutics

OTL-204 for GRN-FTD Section

Frontotemporal Dementia (FTD) Disease Background

- Second most common dementia in people under 65 after Alzheimer's Disease (onset at ~58)
- Atrophy of frontal and temporal lobes
- Progressive changes in behavior and personality:
  - ***Early*** decline in social and personal interactions, depression, apathy, emotional blunting, disinhibition, language disorders
  - ***Late*** general cognitive decline
- Death within 6-9 years from onset, 3-4 years from diagnosis
- No cure or treatment



Orchard therapeutics

GRN-FTD Represents Large and Growing Opportunity

> 50,000 FTD patients diagnosed in U.S. and EU today

THE OPPORTUNITY

GRN-FTD
is a growing opportunity

- Haploinsufficiency of progranulin *(GRN)* strongly associated with FTD (~5% of cases)
- Mutation known to have high penetrance
- Up to 2,500 GRN-FTD prevalent patients in U.S. and EU[1-3]
- ~800 new cases U.S. / EU per year[1-3]

OUR UNIQUE POSITIONING

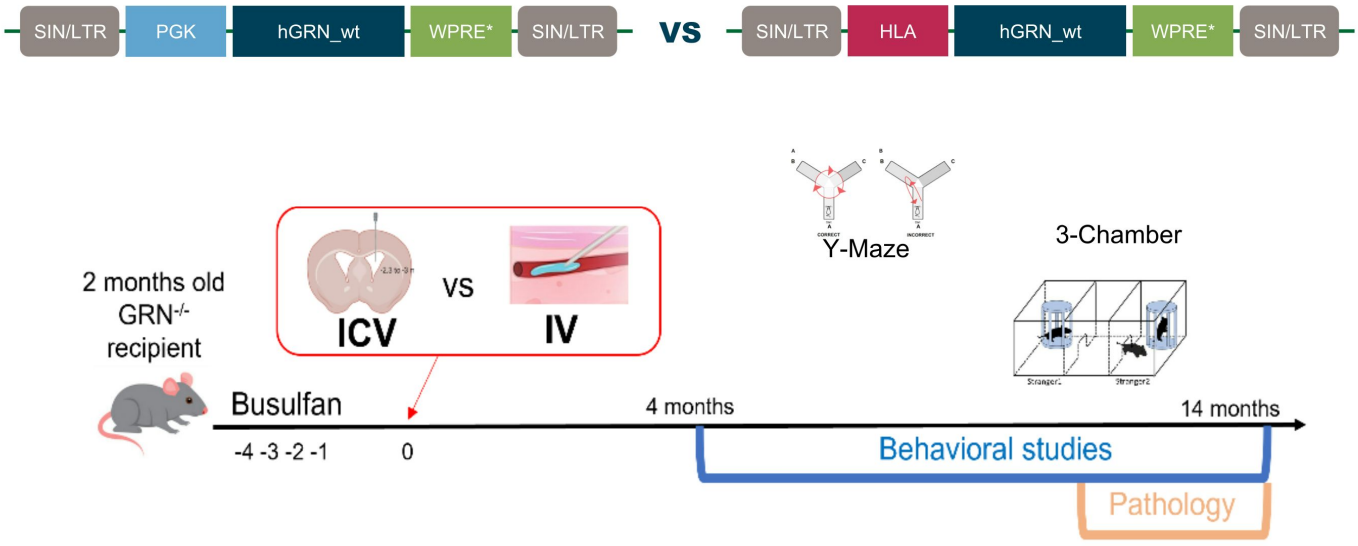
HSC gene therapy has demonstrated potential to treat diseases of the brain

- Ideal for targeting single gene mutations
- Mechanism of CNS gene delivery validated by clinical data from MLD, MPS-I, MPS-IIIA
- Gene-modified HSCs enable delivery of *GRN* to brain

Sources: Knopman DS, Roberts RO. *J Mol Neurosci.* 2011, Onyike CU, Diehl-Schmid J. *Int Rev Psychiatry.* 2013 and Riedl L, et al *Neuropsychiatr Dis Treat.* 2014

Orchard therapeutics

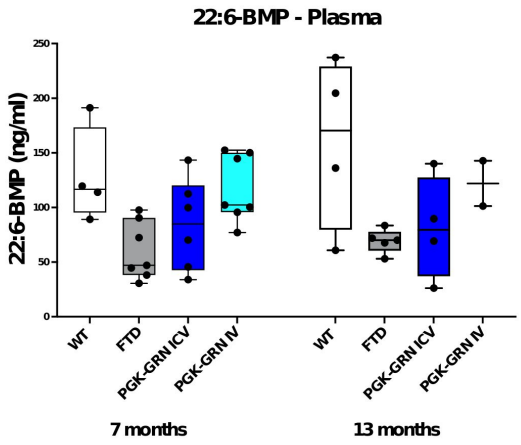
hGRN HSC-GT PoC of efficacy study

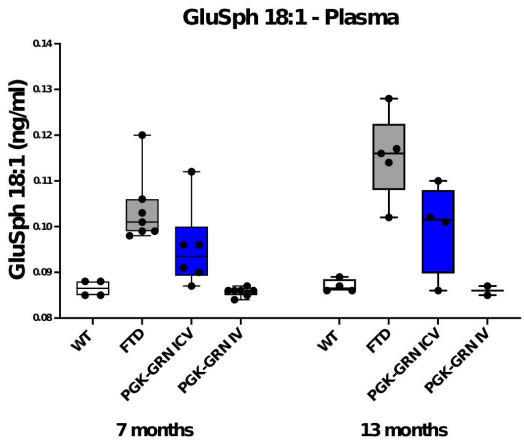


Orchard therapeutics

Therapeutic Effect Evidenced by Normalization of Glucosylsphingosine in Transplanted Mice

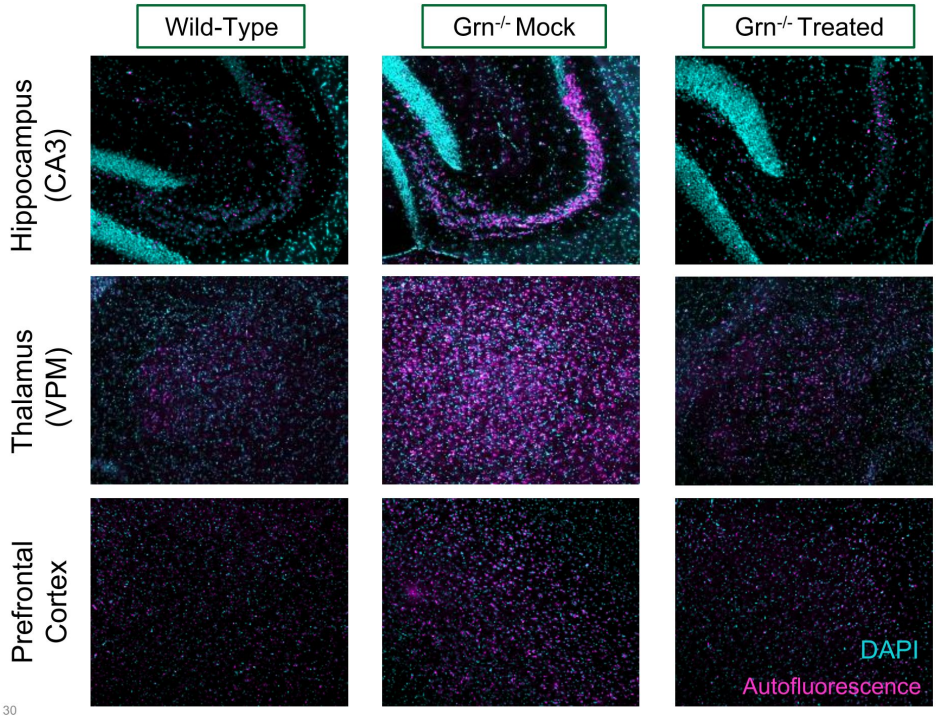
Plasma glycosphingolipid quantification by LC-MS/MS

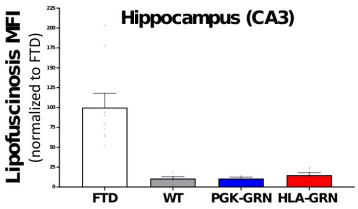


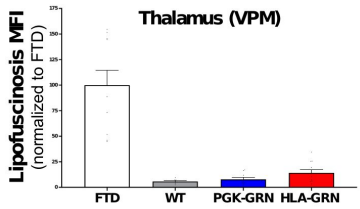


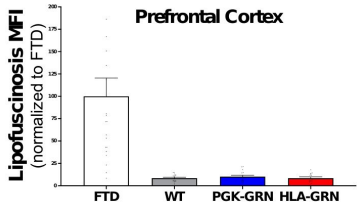
Orchard therapeutics

hGRN improves lipofuscinosis in Knockout Mice



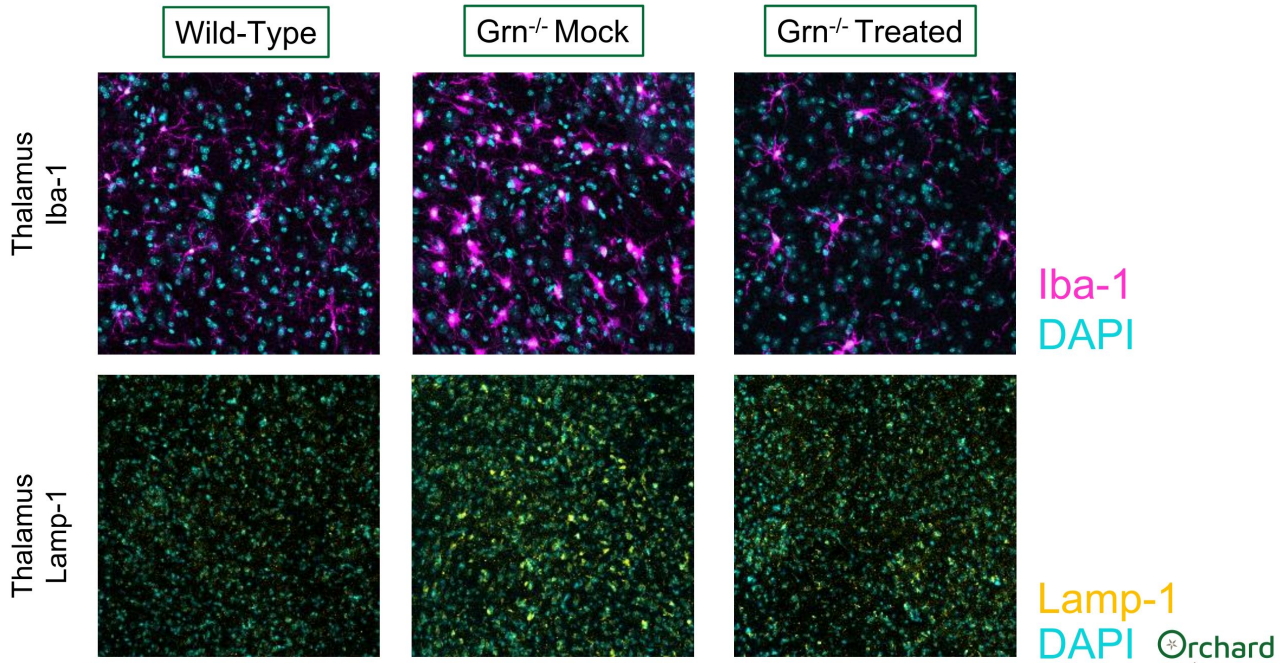






Preliminary data

hGRN reduces microgliosis and Lamp-1 immunoreactivity



Preliminary data

Summary and conclusions

First preclinical data for OTL-204 highlight ability of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers in GRN-FTD

Data from in vivo studies indicate effective GRN protein delivery to the CNS of knockout mice transplanted with gene-modified HSCs.

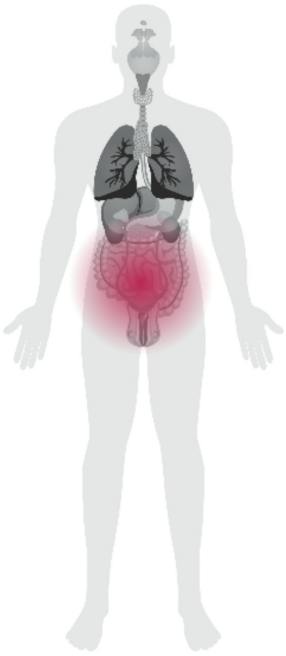
A therapeutic effect in transplanted knockout mice is evidenced by:

- Normalization of glucosylsphingosine, a specific lipid biomarker in the plasma
- Strong reduction of lipofuscinosis and microgliosis
- Decrease of markers of neuroinflammation in the thalamus, hippocampus and prefrontal cortex

Cohorts of knockout mice are being further evaluated both at behavioral and pathological level to accumulate additional evidence supporting the therapeutic approach

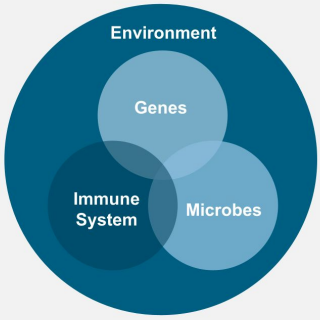
OTL-104 for NOD2-Crohn's Section

Crohn's Disease Overview



- Chronic inflammatory bowel disease
- Primarily affecting ileum
- Symptoms develop from ~15 yrs
- Clinical management by anti-inflammatory medications & surgical resection
- Limited therapies, no cure available
- High prevalence

Contributing causal factors



20-40% of Crohn's patients carry NOD2 mutations

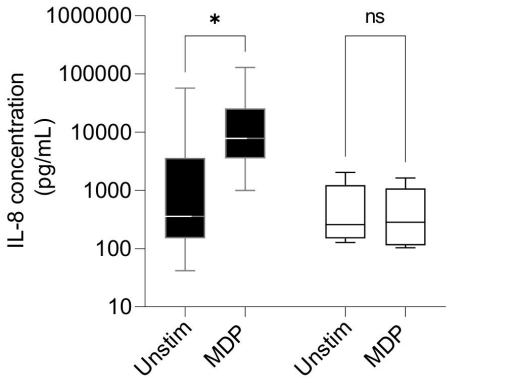
- *NOD2* function: detection of bacterial peptides
- > 60 reported *NOD2* mutations
- 3 SNPs exhibit strongest association
- *NOD2* Crohn's patients are more refractory to therapy & have more severe disease

https://pubmed.ncbi.nlm.nih.gov/28601423/

https://www.biorxiv.org/content/10.1101/098574v2.full
https://www.frontiersin.org/articles/10.3389/fimmu.2016.00367/full

Orchard therapeutics

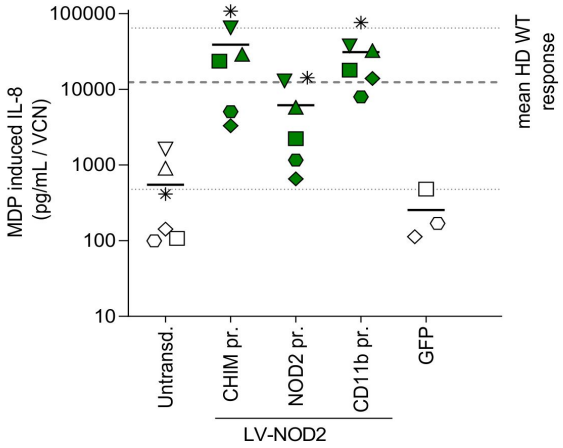
CD34+ HSC derived myeloid cells from NOD2-mutFS CD patients show impaired responses to MDP



Healthy Donors, NOD2 WT (n=9)

Crohn's Disease NOD2mut^{FS} patients (n=5)

Two-way Anova, p<0.05 (*)

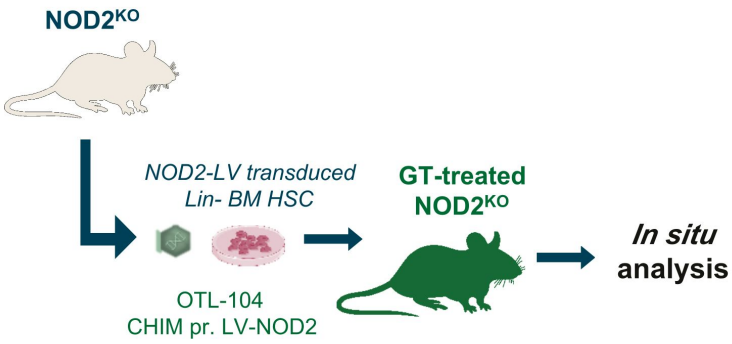


NOD2-mut^{FS} cells +/- LV-GFP

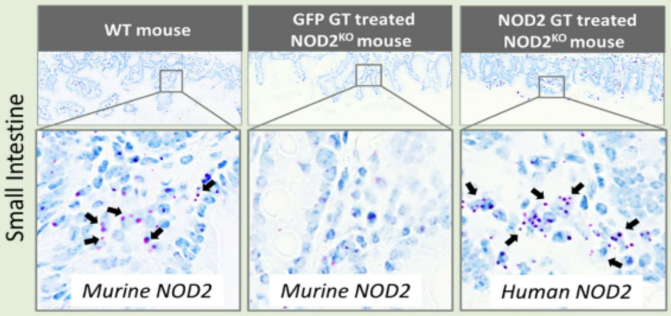
NOD2-mut^{FS} cells + LV-NOD2

Orchard therapeutics

Gene Therapy treatment of NOD2^{KO} mice reconstitutes normal NOD2 expression within the gut and fully restores NOD2-dependent immune responses *in vivo*



Restoration of NOD2 gene expression in intestine

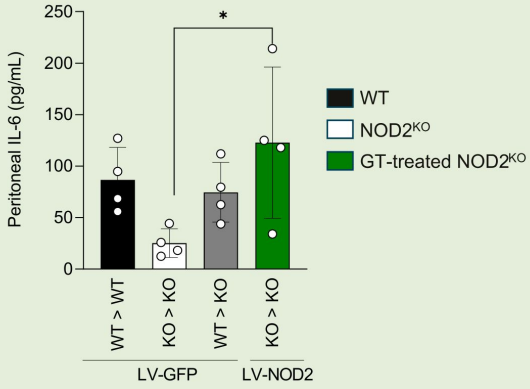


Detection of NOD2 mRNA in situ (RNAScope) in intestinal lamina propria of WT and GT treated NOD2^{KO} mice

Orchard therapeutics

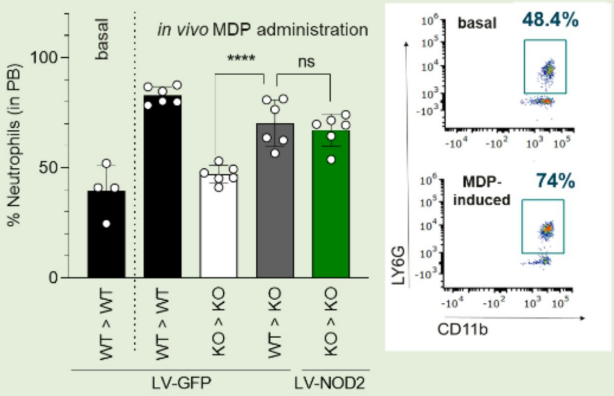
Gene Therapy treatment of NOD2^{KO} mice reconstitutes normal NOD2 expression within the gut and fully restores NOD2-dependent immune responses *in vivo*

Functional reconstitution of NOD2-dependent (MDP-induced) immune activity in myeloid subsets



MDP-induced IL-6 release into peritoneal fluid

Functional reconstitution of NOD2-dependent (MDP-induced) immune activity in myeloid subsets



MDP-induced neutrophil mobilisation

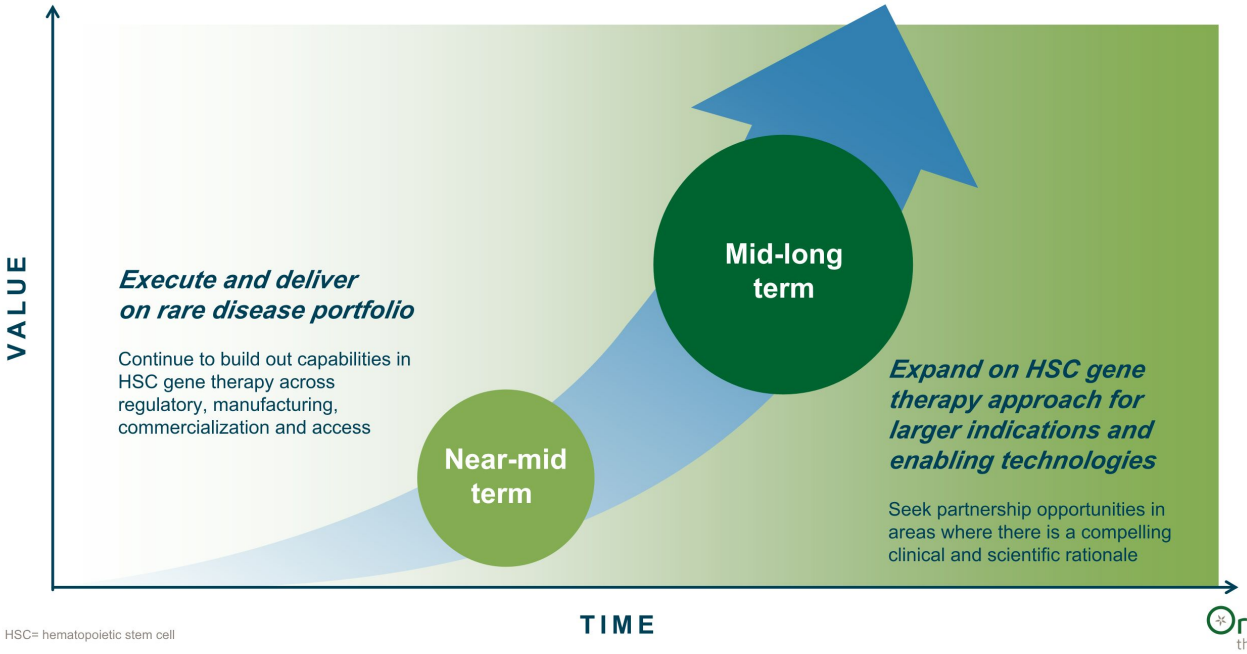
OTL-104 LV-NOD2 CHIM pr. construct shows in vivo efficacy in restoring normal NOD2-dependent myeloid immune functions in GT-treated bone marrow chimeric NOD2^{KO} mice

OTL-104 Summary

- ✓ OTL-104, fully restores NOD2-dependent immune responses in macrophages derived from HSCs obtained from Crohn's patients carrying biallelic NOD2 mutations to within the range of healthy donor cells
- ✓ Transplantation of OTL-104 in NOD2 knockout mice reconstitutes NOD2 expression in intestinal tissue resident cells and broadly restores NOD2-dependent innate immune cell functions
- ✓ Results confirm the negative impact of NOD2 deficiency in primary immune activation and support the therapeutic potential of HSC gene therapy to provide long-term correction of NOD2 Crohn's disease

Expect to commence IND- and CTA-enabling studies in the second half of 2023, with a potential filing anticipated in the first half of 2025

Orchard's Vision to End the Devastation Caused by Severe and other Genetic Diseases



HSC= hematopoietic stem cell

Orchard therapeutics

Key Event Takeaways

OTL-203 for MPS-IH - New PoC data shows extensive metabolic correction in the skeletal system, including normal growth rates, improvement in joint function and progressive acquisition of motor skills

OTL-201 for MPS-IIIA - New data from ongoing PoC study show additional favorable neurocognitive outcomes compared to disease natural history with median follow-up out to 2.5 years

OTL-204 for GRN-FTD - First preclinical data highlighting ability of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers

OTL-104 for NOD2-CD – Preclinical data confirm negative impact of NOD2 deficiency in primary immune activation and support therapeutic potential to provide long-term correction of NOD2 CD

New areas of research could represent significant commercial opportunities in large indications for Orchard alone or with potential partners interested in utilizing HSC gene therapy platform

Orchard therapeutics

Q&A

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

Leslie Meltzer, Ph.D.
Chief Medical Officer

Orchard therapeutics

Exhibit 99.2

Orchard Therapeutics Presents Data from Research Programs at ASGCT Demonstrating the Ability of HSC Gene Therapy to Address Larger Indications

Preclinical proof-of-concept data show the therapeutic potential of OTL-104 for NOD2 Crohn's disease, a severe and treatment-refractory form of the disease

In vivo data demonstrate the development of CAR-Treg cells from genetically engineered HSCs as a potential one-time treatment for autoimmune disorders

Company to host conference call and webcast Tuesday, May 23 at 8:00 a.m. EDT

BOSTON and LONDON, May 18, 2023, (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today presented new data from the company's hematopoietic stem cell (HSC) gene therapy research pipeline targeting larger indications at the ongoing 26th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT) in Los Angeles. Presentations include preclinical proof-of-concept data from OTL-104, the company's investigational HSC gene therapy for the treatment of nucleotide-binding oligomerization domain containing protein 2 (NOD2) Crohn's disease, as well as *in vivo* preclinical data demonstrating the development of functional CAR-Treg cells from genetically engineered HSCs. Both programs were designed and developed in Orchard's own research laboratories utilizing the company's proprietary HSC gene therapy platform.

"These data continue to demonstrate the power of our HSC gene therapy platform and its applicability beyond our rare neurometabolic franchise into diseases with larger patient populations," said Fulvio Mavilio, Ph.D., chief scientific officer of Orchard Therapeutics. "Due to their unique ability to self-renew and differentiate into multiple cell types that migrate to tissues and organs often inaccessible to other therapeutic modalities, HSC-based gene therapies have immense therapeutic and collaborative potential. We look forward to advancing IND-enabling activities for our research program in NOD2 Crohn's disease and further developing the HSC-derived CAR-Treg cell technology."

OTL-104 (NOD2 Crohn's Disease) Preclinical Data Summary

Using established *in vitro* and *in vivo* models of NOD2 deficiency, including NOD2 knockout mice and HSC-derived macrophages from Crohn's patients with biallelic NOD2 mutations, Orchard researchers evaluated the safety and efficacy of HSC gene therapy in restoring NOD2-dependent immune responses. The chimeric promoter used in OTL-104 was originally developed and clinically tested in patients with X-linked chronic granulomatous disease (X-CGD), where enhanced expression of gp91-Phox in myeloid and monocyte lineages was demonstrated.

In a poster session tomorrow, the first preclinical proof-of-concept data will highlight the therapeutic potential of this approach, including:

- OTL-104, a lentiviral vector expressing NOD2 under the control of a myeloid-directed chimeric promoter, fully restores NOD2-dependent immune responses in macrophages derived from HSCs obtained from Crohn's patients carrying biallelic NOD2 mutations to within the range of healthy donor cells.
- Transplantation of OTL-104 in NOD2 knockout mice reconstitutes NOD2 expression in intestinal tissue resident cells and broadly restores NOD2-dependent innate immune cell functions.

Taken together, these results confirm the negative impact of NOD2 deficiency in primary immune activation and support the therapeutic potential of HSC gene therapy to provide long-term correction of NOD2 Crohn's disease. Work to evaluate OTL-104's ability to correct an induced NOD2 knockout mouse model of ileitis is currently ongoing. The company expects to commence IND- and CTA-enabling studies in the second half of 2023, with a potential filing now anticipated in the first half of 2025.

HSC CAR-Treg cell Technology Preclinical Data Summary

Yesterday's poster session demonstrates the feasibility of utilizing HSC gene therapy to provide stable and targeted immunotherapy, through the ability of HSCs to differentiate into T regulatory (Treg) cells engineered to express chimeric antigen-specific receptors (CAR). This approach combines the proven durability of HSC gene therapy with the specific suppressive activity of CAR-Treg cells, providing an alternative to current treatments which fail to effectively control chronic autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis and Type 1 diabetes.

Data from transplanted mice show that the preferential expression of CAR in HSC-derived regulatory T cells *in vivo* does not significantly alter the development, phenotype or function of these suppressive immune cells. Also, the functionality of the CAR receptor is demonstrated when HSC-derived CAR-Tregs can be activated *ex vivo* by exposure to a CAR-specific ligand, producing the immunosuppressive cytokine IL-10.

The company will continue to advance its preclinical research activities aimed at further demonstrating the feasibility and applicability of its HSC CAR-Treg cell technology.

Conference Call and Webcast
A live webcast to recap the data will be available under "News & Events" in the Investors & Media section of the company's website at www.orchard-tx.com on Tuesday May 23, 2023, at 8:00 a.m. EDT. A replay of the webcast will be archived on the Orchard website following the presentation.

About OTL-104 and NOD2 Crohn's Disease
Crohn's disease is a form of Inflammatory Bowel Disease (IBD), a condition affecting the gastrointestinal tract. Mutations in a number of genes are known to confer susceptibility to the risk of Crohn's, and among these the nucleotide-binding oligomerization domain-containing protein 2 (NOD2) gene is the most common genetic factor. NOD2 deficiency results in an impaired detection and clearance of bacteria penetrating the gut during gastrointestinal infection. This leads to a form of Crohn's disease more severe and refractory to existing therapies, with manifestations including chronic abdominal pain, diarrhea, weight loss, fatigue, malnutrition and for some patients, more severe intestinal damage requiring surgical resection. Epidemiological studies suggest NOD2 genetic variants causing functional defects are associated with 7 to 10% of all cases of Crohn's, with up to 200,000 patients in the U.S. and Europe with two NOD2 mutated alleles.

There is currently no cure for Crohn's disease, and long-term, effective treatment options are limited. Current clinical management for Crohn's disease includes use of immune-suppressive medications, biological agents such as anti-TNF, steroids and surgical resection.

OTL-104 is an investigational HSC gene therapy in development for the potential treatment of patients with NOD2 Crohn's disease. As the pathogenesis of NOD2 Crohn's disease is associated with the function of cells of the hematopoietic system, OTL-104 may therefore be used to restore NOD2 function to immune cells such as tissue resident macrophages within the gastrointestinal tract. OTL-104 is designed to introduce the NOD2 gene into cells of the hematopoietic system by lentiviral transduction of a patient's own HSCs, and the gene-modified cells can then be infused back into the patient.

About Orchard's Proprietary HSC T-reg Cell Technology
HSC gene therapy is well-suited to address severe autoimmune disorders due to the ability of HSCs to differentiate into regulatory T-cells (Tregs) which are a specialized subset of T-cells that can suppress inflammation and be harnessed as a cell therapy with an approach similar to that used to create chimeric antigen receptor T-cells (CAR-Ts). Orchard's approach aims to combine the demonstrated durability of HSC gene therapy in genetic diseases with the specific suppressive potential of Tregs. Orchard has established a proprietary position covering the concept, therapeutic application and specifics of HSC-antigen-specific Treg therapy.

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 preclinical, 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.

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 the programs mentioned in this press release, Orchard's expectations with respect to regulatory submissions for its product candidates, 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 will not continue or be repeated in Orchard's ongoing or planned clinical trials, 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 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.

Contacts

Investors
Renee Leck
Senior Director, Investor Relations
+1 862-242-0764
Renee.Leck@orchard-tx.com

Media
Benjamin Navon
Director, Corporate Communications
+1 857-248-9454
Benjamin.Navon@orchard-tx.com

Exhibit 99.3

Orchard Therapeutics Announces Positive Clinical and Preclinical Data in Programs Targeting Neurometabolic and CNS Disorders at ASGCT

New OTL-203 proof-of-concept data demonstrate extensive metabolic correction in the skeletal system of patients with MPS-IH including normal growth rates, improvement in joint function and progressive acquisition of motor skills

Updated OTL-201 data from ongoing proof-of-concept study in MPS-IIIA patients show additional favorable neurocognitive outcomes compared to disease natural history with median follow-up of 2.5 years

First preclinical data for OTL-204 highlight ability of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers in the progranulin form of frontotemporal dementia (GRN-FTD)

Company to host conference call and webcast Tuesday, May 23 at 8:00 a.m. EDT

BOSTON and LONDON, May 19, 2023, (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced multiple clinical and preclinical updates from its portfolio of investigational hematopoietic stem cell (HSC) gene therapies in neurometabolic and neurodegenerative disorders. The data are being featured in several oral presentations at the ongoing 26th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT) in Los Angeles.

“Positive data from multiple clinical and preclinical studies reinforce the ability of our HSC gene therapy platform to drive the migration of gene-corrected cells into the central nervous system and other tissues and deliver therapeutic enzymes and proteins locally to potentially correct multiple severe genetic diseases,” said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard Therapeutics. “The OTL-203 and OTL-201 programs for MPS disorders are intended to address a significant medical need given the limitations or lack of effective therapies for these conditions, and present development and commercial synergies with our neurometabolic pipeline by building on our experience with Libmeldy for metachromatic leukodystrophy. The ability of HSC gene therapy to impact the CNS is further demonstrated by our research program in a genetic subtype of FTD and highlights the potential of our platform to address larger indications.”

OTL-203 (MPS-IH) Skeletal Data Summary

Yesterday’s oral presentation showcased new skeletal data for all eight proof-of-concept trial patients with a median follow-up of 3.78 years, ranging from 3.14 to 4.58 years, compared to a median of two years reported in the November 2021 *New England Journal of Medicine* publication. As previously reported, all eight participants achieved the primary endpoint of supraphysiologic blood alpha-L-iduronidase (IDUA) activity. Growth velocity, cognition and motor function post-treatment were collected as secondary and exploratory endpoints.

At baseline, most patients presented with severe joint range of motion impairment, severe acetabular (hip) dysplasia and varying degrees of dorso-lumbar kyphosis. Treatment with OTL-203 was generally well tolerated and demonstrated extensive metabolic correction over four years after treatment. All patients showed sustained engraftment of gene-corrected cells with blood IDUA activity reaching supraphysiologic levels after treatment and normal or near-normal substrate levels maintained at last follow-up. Persistent IDUA activity and substrate reduction in the cerebrospinal fluid were also seen as of last follow-up, and all patients were able to remain off treatment with enzyme replacement therapy.

In addition:

- All patients exhibited longitudinal growth within expected reference ranges of healthy children according to age and gender, with a median height gain greater than that observed in an external cohort of HSCT patients at three years of follow-up.[i]
- A clinically measurable reduction in both sitting and standing kyphosis was observed in the majority of patients. MRI spine score showed a general stabilization in all patients with no relevant signs of progression in dorso-lumbar kyphosis, vertebrae deformity and dens alterations.
- All patients progressively acquired fine and gross motor skills.
- Improvements in joint range of motion were seen compared to pre-treatment in shoulder flexion, shoulder abduction and hip and knee extension angles as compared with an external cohort of HSCT patients.[i]

The current standard of care for MPS-IH is allogeneic hematopoietic stem cell transplant (HSCT), which does not adequately address the growth and skeletal manifestations of the disease, among other clinical outcomes. Orchard plans to initiate a global 40 patient, registrational, randomized controlled trial compared to standard of care in the second half of 2023.

“MPS-IH is complex multi-system disease that places an enormous burden on affected children and their families,” said Maria Ester Bernardo, M.D., Ph.D. head of the pediatric bone marrow transplantation unit at San Raffaele Hospital and principal investigator of the proof-of-concept study. “The current standard of care, HSCT, is associated with significant morbidity and mortality and does not adequately address some of the more severe manifestations of disease, such as growth and other skeletal issues. These data, which suggest all patients are exhibiting longitudinal growth within expected reference ranges for healthy children adjusted for age and gender, suggest HSC gene therapy has the potential to offer a transformative new treatment approach. We look forward to participating in a global, multi-center registrational trial sponsored by Orchard that will commence later this year.”

OTL-201 (MPS-IIIA) Neurocognitive Data Summary

The oral presentation tomorrow will showcase updated neurocognitive data for all five patients from the ongoing proof-of-concept study, with the median follow-up now extended to 2.5 years (ranging from 18 to 33 months) from a previous median of 1.5 years with a range of 9 to 24 months. At the time of last follow up, the median age of treated patients was 41.6 months (ranging from 30.2 to 53.3 months).

Biochemical data continue to be consistent with previously reported results and demonstrated sustained engraftment, supraphysiological levels of N-sulphoglucosamine sulphohydrolase (SGSH) enzyme and significant reduction of abnormal heparan sulfate levels in all compartments including the central nervous system. Treatment with OTL-201 was generally well-tolerated in the study population. No serious adverse events (SAEs) have been reported as of the recent data cut-off and there has been no evidence of insertional oncogenesis or clonal dominance in samples analyzed to date.

Updated neurocognitive results show:

- With extended follow-up, four out of five patients continued to gain cognitive skills in line with development in healthy children. Two patients were able to progress to a more advanced cognitive test (Kaufman scale, KABC-II), which has not been observed in natural history patients due to progression of disease and cognitive impairment.
- Evidence of developmental gains including acquisition of speech, continence and complex play requiring concentration which are not seen in untreated MPS-IIIA natural history patients was also observed in treated patients.

MPS-IIIA represents a significant medical need given there are no approved therapies and treatment with allogeneic HSCT has not been shown to be effective for this patient population. Patients enrolled in the ongoing proof-of-concept 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 recent follow-up from treated patients provide even more encouraging results for children living with MPS-IIIA and their families, who currently have no effective treatment options,” said Brian Bigger, professor of gene and cell therapy at the University of Manchester (UoM). “With follow-up now extending to more than two years in most patients, we continue to see sustained metabolic correction in the periphery and CNS. The maturing neurocognitive findings continue to suggest modification of the neurological phenotype. Two children have now progressed to the Kaufman scale—a first at Manchester Foundation Trust for MPS-IIIA patients with the severe phenotype.”

OTL-204 (GRN-FTD) Preclinical Data Summary

Today’s oral session is the first presentation supporting preclinical efficacy of OTL-204 in the progranulin form of frontotemporal dementia (GRN-FTD). Orchard, in collaboration with Dr. Alessandra Biffi at the University of Padua (UNIPD), developed therapeutic lentiviral vectors expressing the human GRN gene that were tested and validated using *in vitro* studies.

Data from *in vivo* studies indicate effective GRN protein delivery to the CNS of knockout mice transplanted with gene-modified HSCs. A therapeutic effect in transplanted knockout mice is evidenced by normalization of glucosylsphingosine, a specific lipid biomarker in the plasma, a strong reduction of lipofuscinosis and microgliosis, as well as markers of neuroinflammation in the thalamus, hippocampus and prefrontal cortex. Cohorts of knockout mice are being further evaluated both at behavioral and pathological level to accumulate additional evidence supporting the therapeutic approach.

“These findings highlight the potential of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers in a severe and common form of dementia,” said Fulvio Mavilio, Ph.D., chief scientific officer of Orchard Therapeutics. “Given the unique ability of HSCs to self-renew, differentiate into multiple cell types and cross the blood-brain-barrier, this approach is uniquely suited to potentially provide a one-time, curative treatment for patients and their families. We are encouraged by these positive findings and look forward to further evaluating the behavioral and pathological effects of OTL-204 in this preclinical model.”

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 on Tuesday May 23, 2023, at 8:00 a.m. EDT. Analysts who would like to ask questions at the end of the presentation should register here. A replay of the webcast will be archived on the Orchard website following the presentation.

About OTL-203 and MPS-I
Mucopolysaccharidosis type I (MPS-I) is a rare, inherited neurometabolic disease caused by a deficiency of the alpha-L-iduronidase (IDUA) lysosomal enzyme, which is required to break down sugar molecules called glycosaminoglycans (also known as GAGs). The accumulation of GAGs across multiple organ systems results in multiple symptomatic manifestations of the disease including severe neurocognitive impairment, skeletal deformities, cardiovascular and pulmonary complications, impaired motor function, loss of hearing and corneal clouding. MPS-I occurs at an overall estimated frequency of one in every 100,000 live births. There are three subtypes of MPS-I; approximately 60 percent of children born with MPS-I have the most severe subtype, called Hurler syndrome (MPS-IH), and rarely live past the age of 10 when untreated.

Treatment options for MPS-IH include allogeneic hematopoietic stem cell transplant and chronic enzyme replacement therapy, both of which have limitations. Though early intervention with enzyme replacement therapy has been shown to delay or prevent some clinical features of the condition, it has only limited efficacy on neurological symptoms. OTL-203 is an investigational ex vivo autologous hematopoietic stem cell gene therapy being studied for the treatment of MPS-IH. Orchard was granted an exclusive worldwide license to intellectual property rights to research, develop, manufacture and commercialize the gene therapy program for the treatment of MPS-IH developed by the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy.

About OTL-201 and 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 the sugar molecule heparan sulfate. The buildup of heparan sulfate 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.

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. 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 University of Manchester (UoM). 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 sponsored by UoM, conducted at Royal Manchester Children's Hospital, and funded by Orchard Therapeutics.

About OTL-204 and FTD
Frontotemporal dementia (FTD) refers to a group of disorders caused by progressive damage to neurons in the frontal and temporal lobes of the brain. Symptoms include changes in behavior or personality, emotional problems, trouble communicating, difficulty with work, or difficulty walking. FTD tends to occur at a younger age than other forms of dementia with roughly 60 percent of people with FTD between 45 and 64 years of age, according to the NIH National Institute of Aging.

There is currently no cure or treatment for FTD with mortality occurring 3 to 4 years from diagnosis. Epidemiological studies suggest the FTD prevalent population in the U.S. and Europe is more than 50,000 patients with approximately 5% caused by mutations in the GRN gene, resulting in up to 2,500 GRN-FTD prevalent patients in the U.S. and Europe, with approximately 800 new patients diagnosed each year.

Orchard's preclinical program OTL-204 for GRN-FTD seeks to introduce a working copy of the GRN gene into a person's own HSCs, which can differentiate into microglia and secrete progranulin in the central nervous system, potentially correcting the underlying cause of the disease. Development work in GRN-FTD is being undertaken as part of a collaboration with Prof. Alessandra Biffi, chair of the Pediatric Hematology, Oncology and Stem Cell Transplant Division at the University of Padua (UNIPD).

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.

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 the programs mentioned in this press release, Orchard's expectations with respect to regulatory submissions for its product candidates, 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 will not continue or be repeated in Orchard's ongoing or planned clinical trials, 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 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.

[i] *Schmidt et al. Orphanet Journal of Rare Diseases (2016) 11:93 and Cattoni et al. Mol Genet Metab Rep 2021*

Contacts

Investors
Renee Leck
Senior Director, Investor Relations
+1 862-242-0764
Renee.Leck@orchard-tx.com

Media
Benjamin Navon
Director, Corporate Communications
+1 857-248-9454
Benjamin.Navon@orchard-tx.com