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): **January 11, 2021**

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.)

108 Cannon Street
London EC4N 6EU
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 Global Select 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 2.02 Results of Operations and Financial Condition.

On January 11, 2021, Orchard Therapeutics plc (the "Company") issued a press release announcing a preliminary unaudited estimate of its cash and investments as of December 31, 2020 (the "Financial Information"). A copy of the press release is attached as Exhibit 99.1 to this current report on Form 8-K (the "Report"). The Financial Information is unaudited and does not present all information necessary for an understanding of the Company's financial condition as of December 31, 2020 and its results of operations for the three or twelve months ended December 31, 2020.

The Financial Information contained in Item 2.02 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 (the "Securities Act"), or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 7.01 Regulation FD Disclosure.

The Company intends to participate in the virtual 39th Annual J.P. Morgan Healthcare Conference during the week of January 11, 2021, including holding various investor and analyst meetings and presenting on January 13, 2021 at 9:10 a.m. Eastern Time. A copy of the Company's slide presentation is attached as Exhibit 99.2 to this Report. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.2.

The information contained in Item 7.01 of this Report and Exhibit 99.2 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 January 11, 2021, the Company issued a press release announcing its 2021 strategic priorities. A copy of the press release is attached as Exhibit 99.1 to this Report and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	Description
99.1	Press release dated January 11, 2021
99.2	Presentation of Orchard Therapeutics plc
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: January 11, 2021

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

Orchard Therapeutics Announces 2021 Corporate Priorities Supporting the Build-out of its Commercial Business in Hematopoietic Stem Cell (HSC) Gene Therapy and Expansion of its Clinical Applications

Preparations on Track for First Half 2021 Commercial Launch of Libmeldy™ (OTL-200), the First Approved Product for Metachromatic Leukodystrophy (MLD) in the EU

Filing Strategy for OTL-200 Biologics License Application (BLA) in MLD in the U.S. to be Communicated by Mid-2021 Following Additional Regulatory Interactions

Marketing Authorization Application (MAA) Filing for OTL-103 in Wiskott-Aldrich Syndrome (WAS) on Track for Year End 2021 in the EU; Followed by BLA Filing in 2022 in the U.S.

New Clinical Data for OTL-203 (for MPS-I) and OTL-201 (for MPS-IIIA) Accepted for Oral Presentation at February 2021 WORLD Symposium; Preclinical Data from Research Programs in Larger Indications Expected in 2021

$192M in Cash and Investments to Support Strategic Execution into the First Half of 2022

BOSTON and LONDON, January 11, 2021 (GLOBE NEWSWIRE) – Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today outlined the company's 2021 strategic priorities in advance of its attendance at the virtual 39th Annual J.P. Morgan Healthcare Conference. These priorities support the company's plan of building a successful commercial business in HSC gene therapy and advancing its portfolio of investigational medicines for high-value, high-need indications.

"In a year that challenged how we live and work, I'm extremely proud of Orchard's achievements in 2020," said Bobby Gaspar, M.D., Ph.D., chief executive officer, Orchard Therapeutics. "Our accomplishments were a direct result of the drive and innovation that fuels our commitment to bring our potentially life-saving HSC therapies to patients, including Libmeldy, which is the first product approved for the treatment of eligible patients with early-onset MLD in the EU. With the HSC approach to gene therapy as our scientific foundation, we are focused on the capabilities that can deliver our therapies on a global commercial scale and support our ability to also treat larger indications over time. It has been a privilege to be a pioneer in changing the way medicine is practiced in these conditions, and we look forward to another year of continued execution and scientific progress."

2021 Corporate Priorities
Orchard has outlined the following key corporate objectives and expected milestones for 2021:

1. Build a successful commercial business in HSC gene therapy
    - OTL-200 for MLD:
        - Launch Libmeldy for the treatment of eligible patients with early-onset MLD in the EU in the first half of 2021.

        - By mid-2021, complete interactions with the U.S. Food and Drug Administration (FDA) to determine the path to a BLA filing for OTL-200. The company also expects to receive a decision regarding its regenerative medicine advanced therapy (RMAT) designation application for OTL-200 in the first quarter, which, if granted, has the potential to enhance regulatory interactions and open an expedited path to a BLA filing.
    - OTL-103 for WAS: File an MAA for OTL-103 in the EU by year-end 2021.
2. Continue to lead the development of gene therapies for neurodegenerative disorders by advancing two proof-of-concept (POC) programs in MPS-I and MPS-IIIA
    - OTL-203 for MPS-I: Initiate a registrational trial for OTL-203 by year-end 2021.
    - OTL-201 for MPS-IIIA: Complete enrollment in the five-patient POC trial for OTL-201.
    - POC trial data: Present clinical data from the OTL-203 and OTL-201 POC trials, including two abstracts that have been accepted for oral presentation at the WORLD Symposium in February 2021.
3. Investigate the potential of HSC gene therapy in larger indications
    - Announce new pre-clinical data from research programs in frontotemporal dementia with progranulin mutations (GRN-FTD) and Crohn's disease with mutations in the nucleotide-binding oligomerization domain-containing protein 2 (NOD2-CD) in the second half of 2021.

In preparation for a European launch, Orchard has put in place the commercial infrastructure to support Libmeldy as well as future product launches. The company is qualifying five treatment centers in the UK, Germany, Italy, France and the Netherlands with specialized expertise in transplant and disease area knowledge. In addition, the company expects to leverage cross-border and treatment abroad reimbursement pathways in both Europe and markets such as the Middle East and Turkey. Activities are also underway to drive timely MLD patient identification and access, including disease awareness, genetic testing and newborn screening studies, which have started or are on track to initiate in five countries in 2021.

The company also provided an update concerning the impact of the COVID-19 pandemic on certain development activities. These include restrictions to laboratory access at Orchard and third-party service providers, which is impacting the timeline to develop a specific functional potency assay for OTL-103 in WAS, as requested by the FDA. As a result, the company now expects to file a BLA for OTL-103 in the U.S. in 2022. Orchard is utilizing the benefits provided under OTL-103's RMAT designation and plans to continue interacting with the FDA in 2021 to confirm the data package for the BLA filing. In addition, with several of the follow-up visits associated with the company's active clinical trials impacted by COVID-19 travel restrictions and other trial site limitations, Orchard is using alternative data collection approaches to capture the necessary data to support future regulatory filings.

Frank Thomas, president and chief operating officer continued, "Starting 2021 with a clear set of strategic priorities is crucial to our ability to effectively manage the business while fueling Orchard's continued growth. Our launch preparations for Libmeldy not only mark our evolution towards a fully integrated company but establish a common manufacturing, commercial and operational infrastructure to support multiple future potential products. This work is complemented by our exciting proof-of-concept and research pipeline that we look forward to advancing internally or in partnership."

Key 2020 Achievements
Orchard's key 2020 achievements are highlighted below.

- **CEO transition and strategy update:** Appointed company founder Bobby Gaspar, M.D., Ph.D., as chief executive officer and implemented a new strategic plan to realize the potential of the HSC gene therapy approach.
- **Libmeldy (OTL-200) EU approval:** Received full marketing authorization from the European Commission (EC) for Libmeldy for eligible patients with early-onset MLD.
- **OTL-200 IND submission**: Received FDA clearance for the Investigational New Drug (IND) application for OTL-200 for the treatment of MLD.
- **OTL-203 in MPS-I:** Presented interim data, including clinical outcomes, from the OTL-203 POC trial.
- **OTL-201 in MPS-IIIA:** Dosed the first three patients in the OTL-201 POC trial.
- **Stable cell line technology:** Secured a license for GlaxoSmithKline's proprietary lentiviral stable cell line technology for use in the OTL-103 program in WAS and OTL-300 program in transfusion-dependent beta thalassemia.
- **New research programs:** Announced new research programs in GRN-FTD, NOD2- CD and amyotrophic lateral sclerosis (ALS) at the company's first R&D investor event.

Cash Guidance
The company ended 2020 with approximately $192 million of cash and investments. The company expects that its cash, cash equivalents and marketable securities as of December 31, 2020 will enable the funding of its currently anticipated operating expenses and capital expenditure requirements into the first half of 2022. This excludes the $50 million expected to be available under the company's credit facility and any non-dilutive capital received from potential future partnerships or priority review vouchers.

About Libmeldy / OTL-200

Libmeldy (autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* using a lentiviral vector encoding the human arylsulfatase-A (ARSA) gene), also known as OTL-200, has been approved by the European Commission for the treatment of MLD in eligible early-onset patients characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity in children with i) late infantile or early juvenile forms, without clinical manifestations of the disease, or ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline. Libmeldy is the first therapy approved for eligible patients with early-onset MLD.

The most common adverse reaction attributed to treatment with Libmeldy was the occurrence of anti-ARSA antibodies. In addition to the risks associated with the gene therapy, treatment with Libmeldy is preceded by other medical interventions, namely bone marrow harvest or peripheral blood mobilization and apheresis, followed by myeloablative conditioning, which carry their own risks. During the clinical studies, the safety profiles of these interventions were consistent with their known safety and tolerability.

For more information about Libmeldy, please see the Summary of Product Characteristics (SmPC) available on the EMA website.

Libmeldy is not approved outside of the European Union, UK, Iceland, Liechtenstein and Norway. OTL-200 is an investigational therapy in the US.

Libmeldy was developed in partnership with the San Raffaele-Telethon Institute for Gene Therapy (SR-Tiget) in Milan, Italy.

About Orchard

Orchard Therapeutics is a global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. In 2018, Orchard 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. Orchard now has one of the deepest and most advanced gene therapy product candidate pipelines in the industry spanning multiple therapeutic areas where the disease burden on children, families and caregivers is immense 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 certain forward-looking statements about Orchard's strategy, future plans and prospects, which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include express or implied statements relating to, among other things, Orchard's business strategy and goals, including its plans and expectations for the commercialization of Libmeldy, the therapeutic potential of Libmeldy (OTL-200) and Orchard's product candidates, including the product candidates referred to in this release, 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, the likelihood that data from clinical trials will be positive and support further clinical development and regulatory approval of Orchard's product candidates, and Orchard's financial condition and cash runway into the first half of 2022. 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 Libmeldy will not continue or be repeated in our ongoing or planned clinical trials of Libmeldy, will be insufficient to support regulatory submissions or marketing approval in the US or to maintain marketing approval in the EU, or that long-term adverse safety findings may be discovered; the risk that any one or more of Orchard's product candidates, including the product candidates referred to in this release, will not be approved, successfully developed or commercialized; the risk of cessation or delay of any of Orchard's ongoing or planned clinical trials; the risk that Orchard may not successfully recruit or enroll a sufficient number of patients for its clinical trials; the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical studies or clinical trials will not be replicated or will not continue in ongoing or future studies or trials involving Orchard's product candidates; the delay of any of Orchard's regulatory submissions; the failure to obtain marketing approval from the applicable regulatory authorities for any of Orchard's product candidates or the receipt of restricted marketing approvals; the inability or risk of delays in Orchard's ability to commercialize its product candidates, if approved, or Libmeldy, including the risk that Orchard may not secure adequate pricing or reimbursement to support continued development or commercialization of Libmeldy; the risk that the market opportunity for Libmeldy, or any of Orchard's product candidates, may be lower than estimated; and the severity of the impact of the COVID-19 pandemic on Orchard's business, including on clinical development, its supply chain and commercial programs. 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 quarterly report on Form 10-Q for the quarter ended September 30, 2020, as 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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Vice President, Corporate Affairs
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media@orchard-tx.com

Exhibit 99.2

Orchard therapeutics

2021 JP Morgan Presentation

Bobby Gaspar, M.D., Ph.D.
Chief executive officer

January 13, 2021

Forward Looking Statements

Certain information set forth in this presentation and in statements made orally during this presentation contains "forward-looking statements". Except for statements of historical fact, information contained herein constitutes forward-looking statements and may include, but is not limited to, the Company's expectations regarding: (I) the safety and efficacy of Libmeldy and its product candidates; (II) the expected development of the Company's business and product candidates; (III) the timing of regulatory submissions for approval of its product candidates; (IV) the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates; (V) the timing of announcement of preclinical and clinical data for its product candidates and the likelihood that such data will be positive and support further development and regulatory approval of these product candidates; (VI) the timing and likelihood of approval of such product candidates by the applicable regulatory authorities; (VII) the adequacy of the Company's supply chain and ability to commercialize Libmeldy, including the ability to secure adequate pricing and reimbursement to support continued development and commercialization of Libmeldy; (VIII) execution of the Company's vision and growth strategy, including with respect to global growth; (IX) the size and value of potential markets for the Company's product candidates; and (X) projected financial performance and financial condition, including the sufficiency of the Company's cash and cash equivalents to fund operations in future periods and future liquidity, working capital and capital requirements. The words "may," "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "potential," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements are provided to allow investors the opportunity to understand management's beliefs and opinions in respect of the future so that they may use such beliefs and opinions as one factor in evaluating an investment.

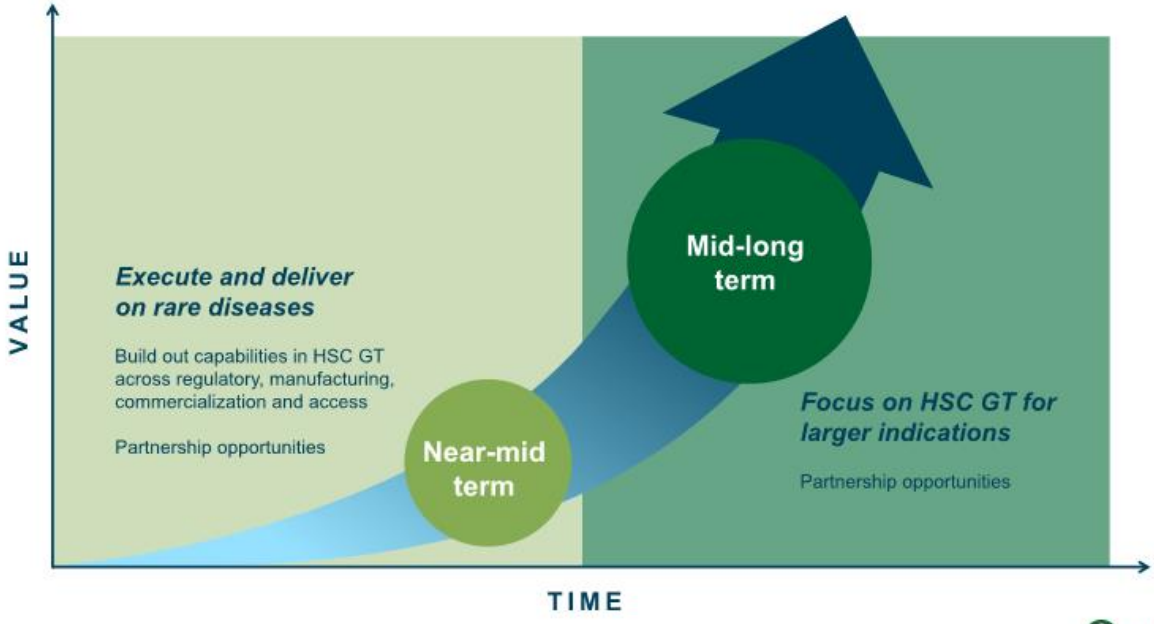
These statements are neither promises nor guarantees of future performance. Such forward-looking statements necessarily involve known and unknown risks and uncertainties, which include, without limitation, the severity of the impact of the COVID-19 pandemic on the Company's business, including on preclinical and clinical development and commercial programs, which may cause actual performance and financial results in future periods to differ materially from any projections of future performance or results expressed or implied by such forward-looking statements. You are cautioned not to place undue reliance on forward-looking statements. These statements are subject to a variety of risks and uncertainties, many of which are beyond the Company's control, which could cause actual results to differ materially from those contemplated in these forward-looking statements. For additional disclosure regarding these and other risks faced by the Company, see the disclosure contained in the Company's public filings with the U.S. Securities and Exchange Commission (the "SEC"), including in the Company's quarterly report on Form 10-Q filed with the SEC on November 3, 2020, as well as subsequent filings and reports filed with the SEC. These forward-looking statements speak only as of the date of this presentation. The Company undertakes no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

Curing the incurable

The potential of HSC gene therapy

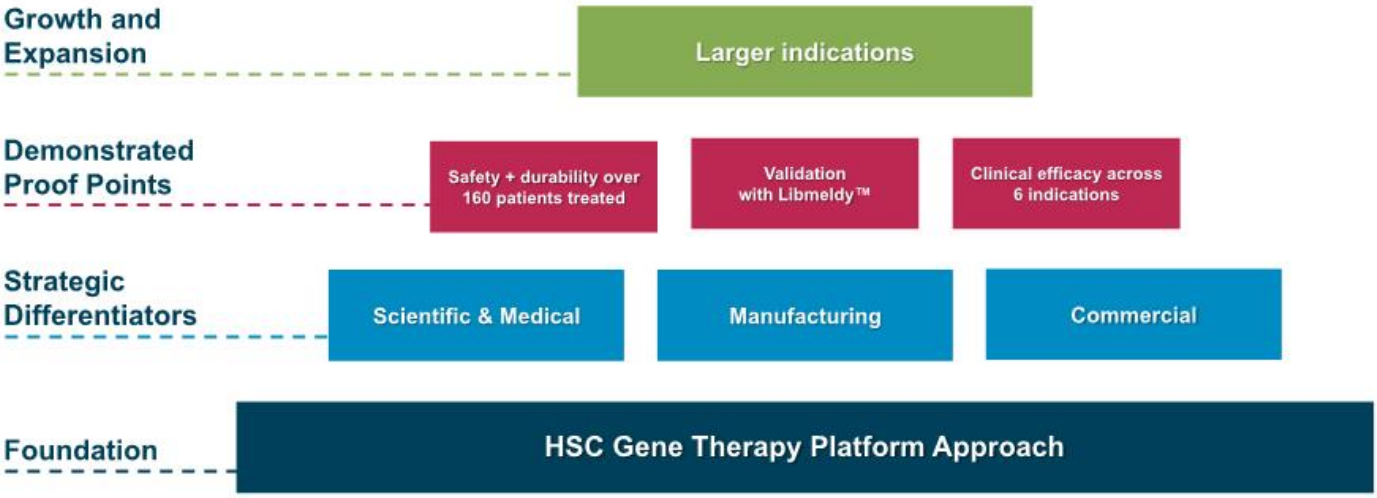
Orchard therapeutics

A Vision for Long-term Growth and Value Creation



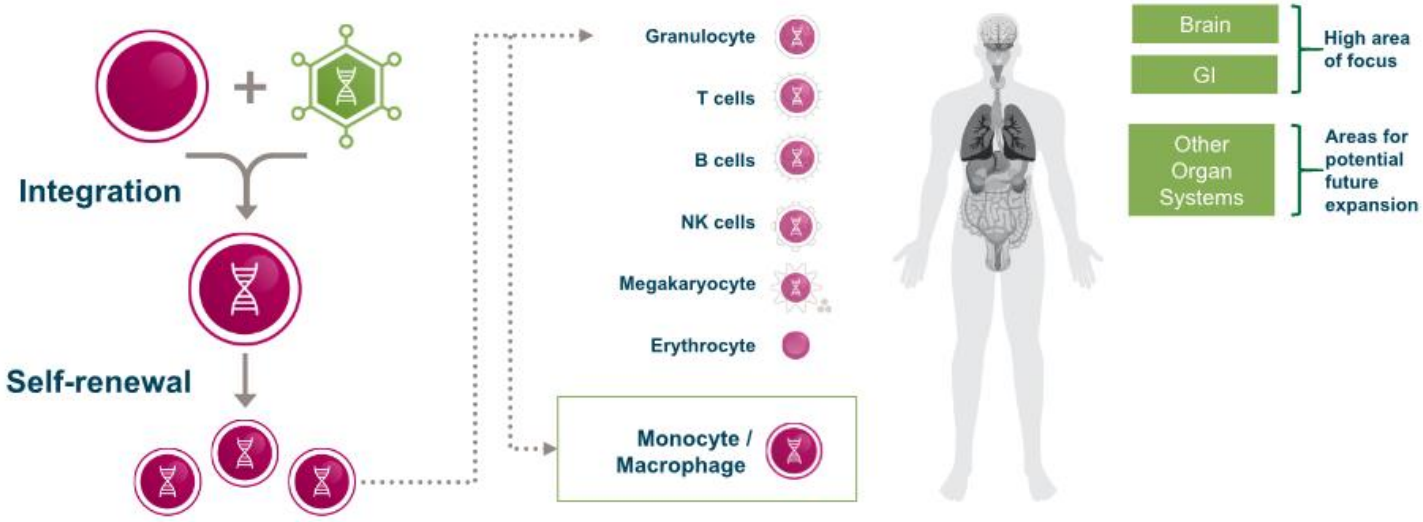
Orchard therapeutics

We Are Delivering Now and Building for the Future



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

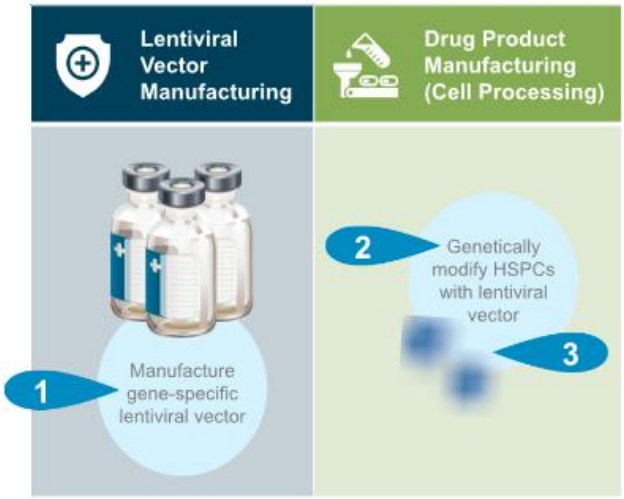
Orchard therapeutics

Durability of Response and Safety Demonstrated via Longest Patient Follow-up

Patients treated in the development phase, including in clinical trials and under pre-approval access (defined as any form of pre-approval treatment outside of a company-sponsored clinical trial, including, but not limited to, compassionate use, early access, hospital exemption or special license).
Data based on in-house data as of November 2020. Data include all patients treated with CD34+ hematopoietic stem cells transduced ex vivo with vector of interest.

Orchard therapeutics

Improving the HSC Gene Therapy Manufacturing Process



	Technology innovations
1 Vector Production	Scalable suspension culture with stable producer cell line
2 Stem Cell Transduction	Transduction enhancing compounds
3 Drug product process	Fully closed, automated cell processing

 | HSPC = Hematopoietic stem and progenitor cell

Orchard therapeutics

Applying Commercial Strategy to Launch Gene Therapies Globally

Leverage for Libmeldy and future launches

Enable Patient ID & Diagnostics

Multi-pronged diagnostics initiatives and newborn screening in EU and U.S.

Expand Geographic Footprint

Qualifying leading centers with transplant and disease area experience

Establish Global Supply Network

Inventory, capacity and logistics of supply

Secure Market Access

Multi-stakeholder engagement with flexible payment models

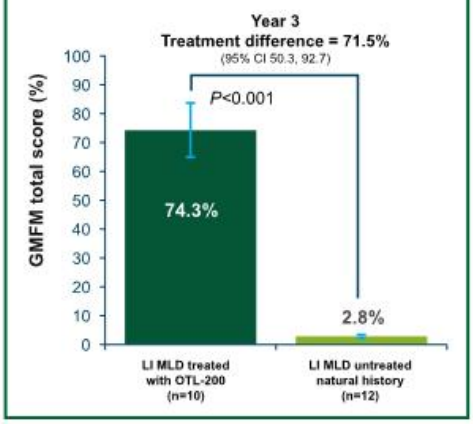
Orchard therapeutics

HSC Gene Therapy: Meeting the Need in Severe Neurodegenerative Disorders

Orchard therapeutics

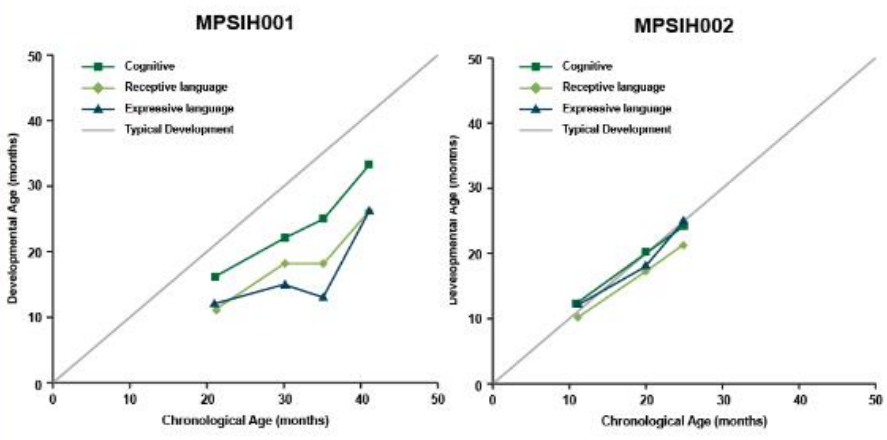
Clinical Efficacy in Multiple Devastating, Rapidly Progressive Diseases

Late Infantile MLD



LI, late infantile; EJ, early juvenile CI, confidence interval; GMFM, gross motor function measurement; MLD, metachromatic leukodystrophy;
Both LI and EJ patients (EJ not shown) achieved a statistically significant difference on the co-primary endpoint of improvement of >10% of the total GMFM score in treated subjects when compared to the Natural History cohort at Year 2, and these were maintained through Year 3. Note: vertical error bars are standard error of the adjusted mean. P-values are from a two-sided 5% hypothesis test with null hypothesis of ≤ 10% difference

MPS-I



MPS-I data presented May 15, 2020 at ASGCT annual meeting

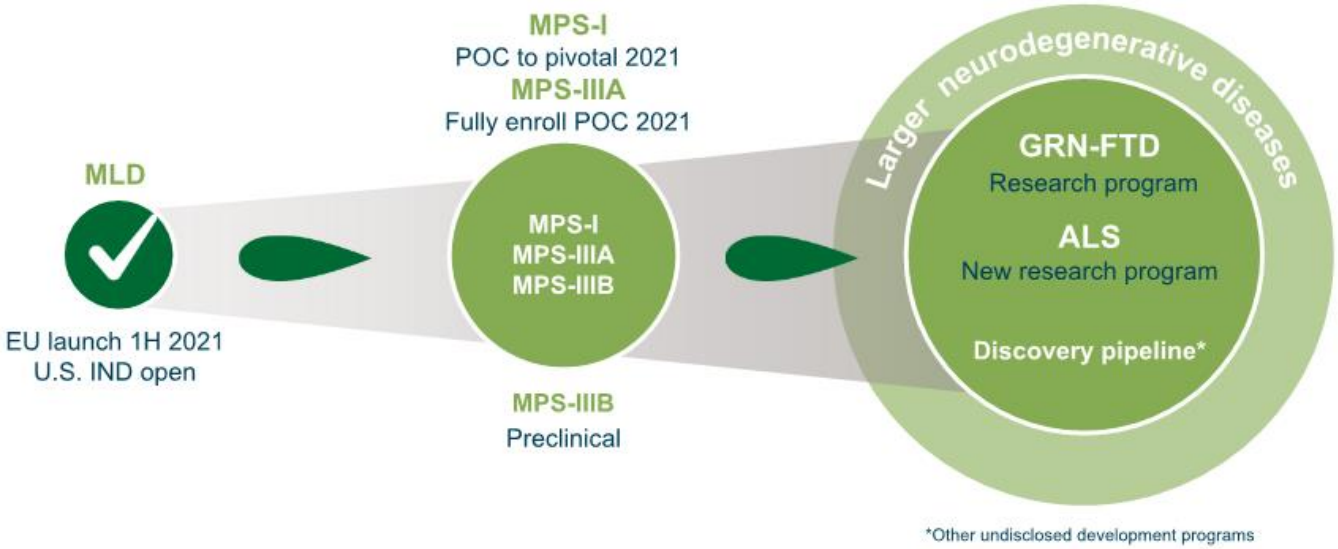
Orchard therapeutics

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

Nine Orchard Abstracts Accepted Showcasing Strength of HSC Approach

OTL-203 for MPS-I	**New clinical results from fully enrolled POC trial**
OTL-201 for MPS-IIIA	**Results from first three patients treated**
OTL-200 for MLD	**NBS, market access and cryopreservation data**

Growing Neurodegenerative Portfolio from Rare to Larger Indications



*Other undisclosed development programs

Orchard therapeutics

HSC Gene Therapy Is Highly Suited for GRN-FTD: a Large and Growing Opportunity

THE OPPORTUNITY

OTL-204 for GRN-FTD

- 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 preclinical and clinical data from MLD, MPS-I, MPS-IIIA
- Gene-modified HSCs enable delivery of *GRN* to brain

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

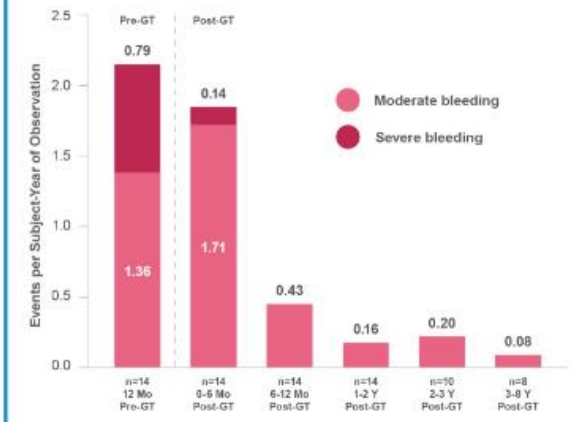
Orchard therapeutics

HSC Gene Therapy: Advancing the Treatment Landscape in Immunological Disorders

Orchard therapeutics

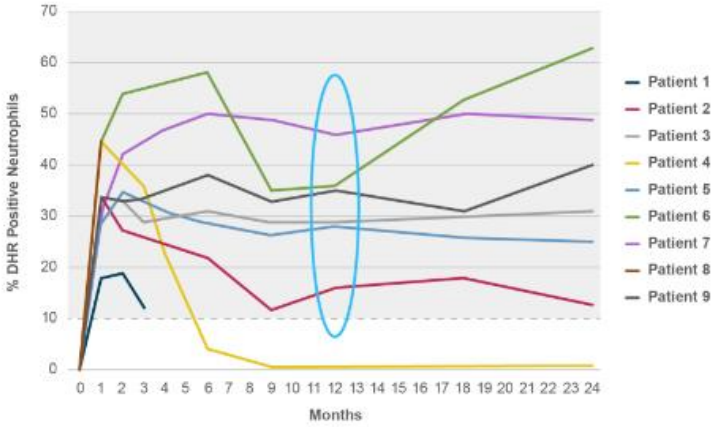
Compelling Evidence in Immunological Disorders

OTL-103 for WAS
Moderate or severe bleeds



Elimination of severe bleeds

OTL-102 for X-CGD
Oxidase Activity



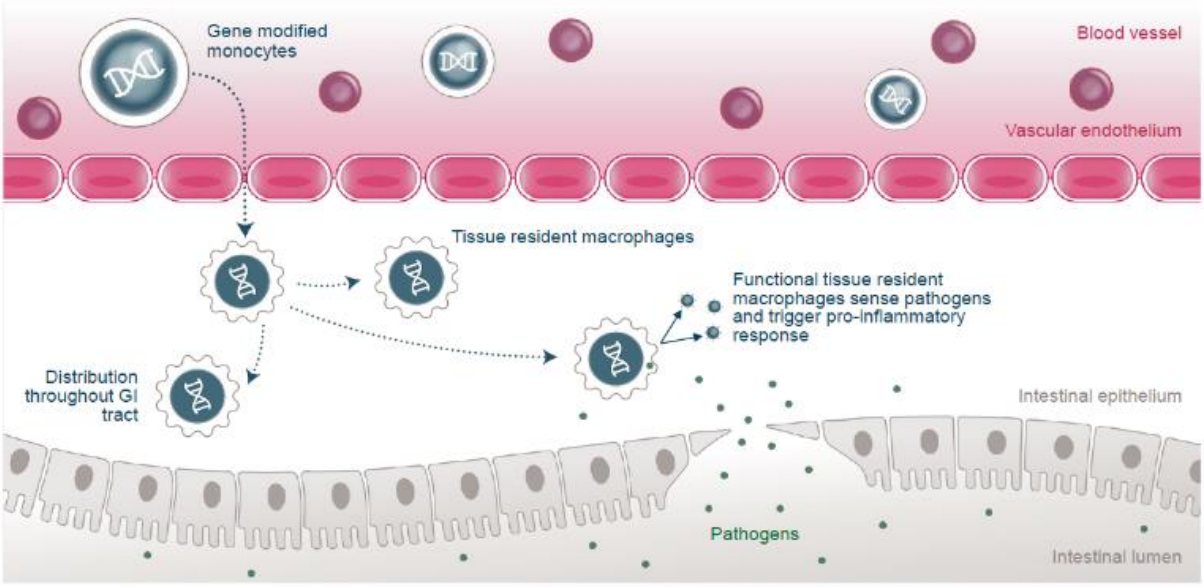
Functional neutrophils (above 10%) in 6 of 7 patients

Data presented at ASH 2019
Events per patient-year of observation for each observation period; GT, gene therapy; mo, months, N, number of patients; Y, years

Data published January 2020 in Nature Medicine
† patient deceased from advanced disease; Excludes data from 1 patient treated with drug product deemed by the investigator to be different from the OTL-102 drug product

Orchard therapeutics

HSC Transplants Give Rise to Tissue Macrophages with the Potential to Reconstitute Functional Gut Innate Immunity



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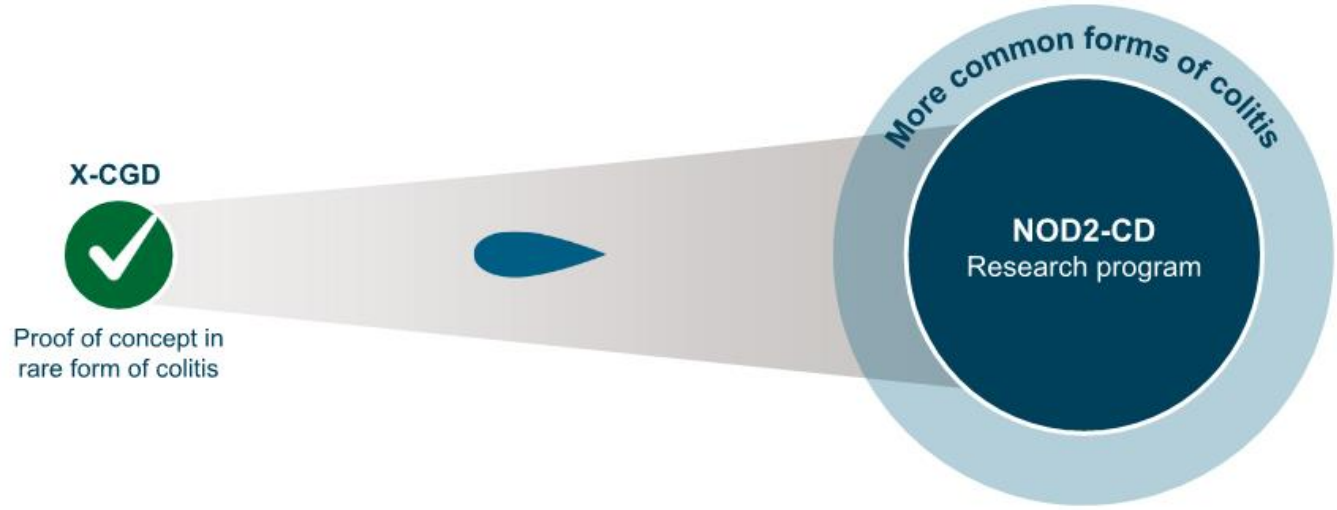
Clinical Validation in X-CGD Supports Application in Larger Populations such as NOD2 Crohn's Disease



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OTL-104 for NOD2-Crohn's Represents a Significant Commercial Opportunity

THE OPPORTUNITY

NOD2-Crohn's
is a significant segment of Crohn's disease

- Up to 200,000 estimated patients with two mutated NOD2 alleles (7-10% of all Crohn's disease) in the U.S. and EU[1,2,3]
- NOD2-CD is increasingly recognized as a monogenic form of CD

OUR UNIQUE POSITIONING

Demonstrated potential of HSC gene therapy to treat other forms of colitis

- HSC GT and HSCT correct colitis in X-CGD + other monogenic PIDs
- NOD2-CD disorder of monocytes / macrophages in GI wall
- NOD2 patients often have severe relapsing disease despite immunosuppressive therapy
- Severe CD already associated with need for autologous HSCT

[1,2] CD prevalence estimates: Centers for Disease Control and Prevention; European Crohn's and Colitis Organisation (ECCO)
[3] NOD2: Ashton, James J et al.Clin Transl Gastroenterol. 2020 Feb

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Operations and Upcoming Milestones

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Today's Roadmap for a Sustainable Future

1	**Maintain Strong Balance Sheet**	• YE 2020 cash of $192M • Access equity markets following inflection points • Supplement with non-dilutive capital
2	**Invest for Growth**	• Focus on highest value programs • Allocate R&D capital for larger indications • Stage investments in additional rare disease programs
3	**Leverage Partnership Opportunities**	• Evaluate based on disease expertise and commercial footprint • Leverage HSC GT platform as engine for new indications

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2021 is Rich in Expected Milestones Spanning Development and Commercialization

Preclinical	Clinical	Regulatory	Commercial
OTL-204: Announce data from GRN-FTD research program **OTL-104:** Announce data from NOD2-CD research program	**OTL-203:** Initiate registrational study for MPS-I **OTL-201:** Complete enrollment in MPS-IIIA POC study Present interim data from **OTL-201** and **OTL-203** POC studies	**OTL-200:** Determine BLA filing strategy for MLD by mid-2021 **OTL-103:** Submit MAA filing for WAS by year-end 2021	**Libmeldy / OTL-200:** Launch in EU 1H 2021 **Libmeldy / OTL-200:** Leverage cross-border and treatment abroad reimbursement pathways in Europe, Middle East and Turkey

Building a fully integrated company

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Compelling Fundamentals Driving Near and Long-term Growth

- **1x treatment** – HSC gene therapy approach offers curative potential
- **Strong clinical track record** – over 160 patients treated
- **Clinical validation** in rare diseases increases confidence for larger indications

libmeldy™▼
(Autologous CD34+ cells encoding ARSA gene)

now approved for early-onset MLD in the EU

$192M in cash as of YE 2020 and runway into the first half of 2022

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