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 10, 2022**

ORCHARD THERAPEUTICS PLC

(Exact name of Registrant as Specified in Its Charter)

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

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 10, 2022, Orchard Therapeutics plc (the "Company") issued a press release announcing a preliminary unaudited estimate of its cash and investments as of December 31, 2021 (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, 2021 and its results of operations for the three or twelve months ended December 31, 2021.

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 40th Annual J.P. Morgan Healthcare Conference during the week of January 10, 2022, including holding various investor and analyst meetings and presenting on January 13, 2022 at 9:00 a.m. Eastern time. A copy of the Company's 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 10, 2022, the Company issued a press release announcing its 2022 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 10, 2022
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 10, 2022

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

Exhibit 99.1

Orchard Therapeutics Announces Recent Commercial and Regulatory Progress for Late-stage HSC Gene Therapy Programs and Outlines Key 2022 Milestones

Launch Momentum Building for Libmeldy® in Europe with Health Technology Assessments Progressing Favorably and Treatment Underway for Multiple Commercial Patients

Initiating U.S. BLA Submission for OTL-200 as Early as Year End 2022; Constructive CMC Meeting with FDA Supports Timeline

EU MAA Submission for OTL-103 in Wiskott-Aldrich Syndrome Expected in Mid-2022 Following Productive Regulatory Interactions

Ended 2021 with approximately $220M in Cash and Investments to Support Operations into the First Half of 2023

BOSTON and LONDON, January 10, 2022 (GLOBE NEWSWIRE) – Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today outlined commercial and regulatory updates and key 2022 milestones in advance of its attendance at the virtual 40th Annual J.P. Morgan Healthcare Conference. These activities and priorities support the company's vision to end the devastation caused by genetic and other severe diseases through the curative potential of HSC gene therapy.

"Looking back at 2021 Orchard has accomplished much, from significant progress in the launch of Libmeldy in Europe, to receiving clarity from regulators on the potential path forward for our MLD, WAS and MPS-IH programs, as well as showcasing new discovery projects through our HAE collaboration with Pharming and at our latest R&D Day," said Bobby Gaspar, M.D., Ph.D., chief executive officer. "There is still work to do, and we are starting 2022 with the same passion and commitment to continue building a company focused on changing the treatment paradigm for patients with severe genetic diseases."

Libmeldy Commercial Updates in Europe

As part of Orchard's objective to build a successful and sustainable commercial business in HSC gene therapy, the company is focused on three foundational pillars of the Libmeldy launch: market access, patient identification and treatment delivery.

- Market access: Health technology assessments (HTAs) are progressing well across Europe. The company is pleased that the HTA bodies have recognized both the severity of MLD and the magnitude of potential therapeutic benefit of Libmeldy to treat this condition. For example, in Germany, Libmeldy is one of only five medicines to ever achieve the highest possible therapeutic benefit rating of "major benefit" for pre-symptomatic MLD patients. Orchard anticipates reaching reimbursement agreements with at least two countries in the first half of 2022.
- Patient identification: Patient identification efforts are progressing well, and two patients, one in France and one in Germany, are in the process of being treated commercially with Libmeldy under reimbursed early access. Activities are also underway to drive a timely MLD diagnosis, including five newborn screening studies or pilots that have launched or are planned in Germany, Italy, the UK, Spain and France.

- Treatment delivery: Four centers with specialized expertise in transplant and disease area knowledge in Germany, Italy, France and the Netherlands are treatment-ready and activation of a fifth center in the UK is in progress.

“As leaders in the field of HSC gene therapy, we are pioneering all aspects of our operations—including how we commercialize and deliver these potentially transformative medicines to the communities we serve,” said Braden Parker, chief commercial officer. The foundation and experience we are establishing for this launch will serve us well in 2022 and beyond as we expand geographically.”

Regulatory Progress and Upcoming Milestones for OTL-200 and OTL-103

OTL-200 for MLD (U.S.)
Orchard has completed the majority of the activities necessary in advance of a pre-Biologics License Application (BLA) meeting with U.S. Food and Drug Administration (FDA) for OTL-200. In December 2021, a Type B CMC meeting took place with the FDA, the feedback from which confirms a planned BLA submission timeline of late 2022 to early 2023.

OTL-103 for WAS (EU and U.S.)
Following productive regulatory interactions with the European Medicines Agency (EMA) and recent rapporteur and co-rapporteur meetings, Orchard is preparing for a Marketing Authorization Application (MAA) submission for OTL-103 in Europe in mid-2022. In the U.S., Orchard is planning to interact with FDA in early 2022 to discuss elements of a potential BLA filing package, including development work on a functional potency assay and the clinical dataset.

Orchard is utilizing the benefits provided under FDA’s regenerative medicine advanced therapy (RMAT) designation for both OTL-103 and OTL-200’s regulatory interactions in the U.S.

Additional 2022 Corporate Priorities

To lead the development of gene therapies for neurodegenerative disorders and investigate the potential of HSC gene therapy in future indications where there is a compelling scientific and clinical rationale, Orchard has outlined the remaining key milestones expected for 2022:

- OTL-203 for MPS-IH: Obtain the necessary regulatory clearance in mid-2022 to enable the initiation of the OTL-203 global registrational study in MPS-IH by year end.
- OTL-201 for MPS-IIIA: Present clinical data, including early clinical outcomes of cognitive function, from the OTL-201 proof-of-concept (POC) trial in the first half of 2022.
- Research programs: Advance the company’s preclinical portfolio, which includes programs focused on neurodegenerative disorders (OTL-204 for GRN-FTD and OTL-205 for ALS), immunological diseases (OTL-104 for NOD2-CD and OTL-105 for HAE) and HSC-generated antigen-specific Tregs.

Key 2021 Achievements
Orchard’s key achievements from 2021 are highlighted below.

- **Libmeldy (MLD) Europe:**
  - Initiated launch activities including market access discussions and qualifying treatment centers.

    - Established partnerships to identify eligible patients for Libmeldy in the Middle East and Turkey.
- **OTL-200 (MLD) U.S:**
    - Received clarity from FDA on the expected clinical and CMC package for a BLA.
    - Manufactured OTL-200 for use under investigator-initiated compassionate use Investigational New Drug (INDs) at the University of Minnesota, the first clinical site to administer OTL-200 outside of Europe. Orchard also coordinated the successful shipment and release of patients' HSCs between the U.S. treatment site and ACG Biologics' manufacturing facility in Italy.
- **OTL-203 (MPS-IH):**
    - Presented one-year POC data, including clinical outcomes of cognitive function, motor function and growth.
    - Obtained guidance on the design of a global registrational trial through a parallel scientific advice meeting with FDA and EMA.
- **OTL-201 (MPS-IIIA):** Completed enrollment of five patients in the POC trial and presented initial study data.
- **Research and discovery:**
    - Signed a strategic collaboration with Pharming Group N.V. to research, develop, manufacture and commercialize OTL-105, an investigational ex vivo autologous HSC gene therapy for the treatment of hereditary angioedema (HAE).
    - Hosted a virtual R&D event highlighting updates from the OTL-104 program for NOD2 Crohn's disease (NOD2-CD) and potential new applications in HSC-generated antigen-specific regulatory T-cells (Tregs) and HSC-vectorization of monoclonal antibodies.
- **Publications:** Supported two New England Journal of Medicine (NEJM) publications, including interim proof-of-concept results for the OTL-203 program in MPS-IH.
- **Cash position:** Raised $150 million in a strategic financing through a private investment in public equity (PIPE) financing.

Cash Guidance
The company ended 2021 with approximately $220 million of cash and investments. The company expects that its cash, cash equivalents and investments as of December 31, 2021 will support its currently anticipated operating and capital expenditure requirements into the first half of 2023. This cash runway excludes an additional $67 million that could become available under the company's credit facility and any non-dilutive capital received from potential future partnerships or priority review vouchers granted by the FDA following future U.S. approvals.

About Libmeldy / OTL-200

Libmeldy (atidarsagene autotemcel), 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 approved in 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

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 GlaxoSmithKline (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 has a deep 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 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 2023. 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, 2021, 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.

Contacts

Investors
Renee Leck
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 99.2

Reaching New Heights, Looking to New Horizons

Bobby Gaspar, M.D., Ph.D., *chief executive officer*

40th Annual J.P. Morgan Healthcare Conference

January 13, 2022

From Clinician to CEO: The Evolution of HSC Gene Therapy

Photo courtesy of Great Ormond Street Hospital

We aspire to end the devastation caused by genetic and other severe diseases through the curative potential of HSC gene therapy.

2021 Progress and Achievements Lays Strong Foundation for 2022

MLD	✓ **Libmeldy® (Europe):** Initiated commercial launch activities and multiple NBS pilots ✓ **OTL-200 (U.S.):** Received clarity from FDA on the expected clinical and CMC package for a BLA
MPS	**OTL-203 (MPS-IH):** ✓ Presented one-year proof-of concept data, including cognitive/motor function and growth ✓ Obtained regulatory guidance on design of a global registrational trial **OTL-201 (MPS-IIIA):** ✓ Completed enrollment of five patients in proof-of-concept trial; presented initial study data
R&D	✓ **OTL-105 (HAE):** Signed a strategic collaboration with Pharming Group N.V.

Ended 2021 with approximately $220M of cash and investments; runway into 1H'23

Libmeldy is approved in the European Union, UK, Iceland, Liechtenstein and Norway. OTL-200 is an investigational therapy in the US.

2022: Reaching New Heights, Looking to New Horizons

Reaching New Heights

Looking to New Horizons

The Journey Ahead

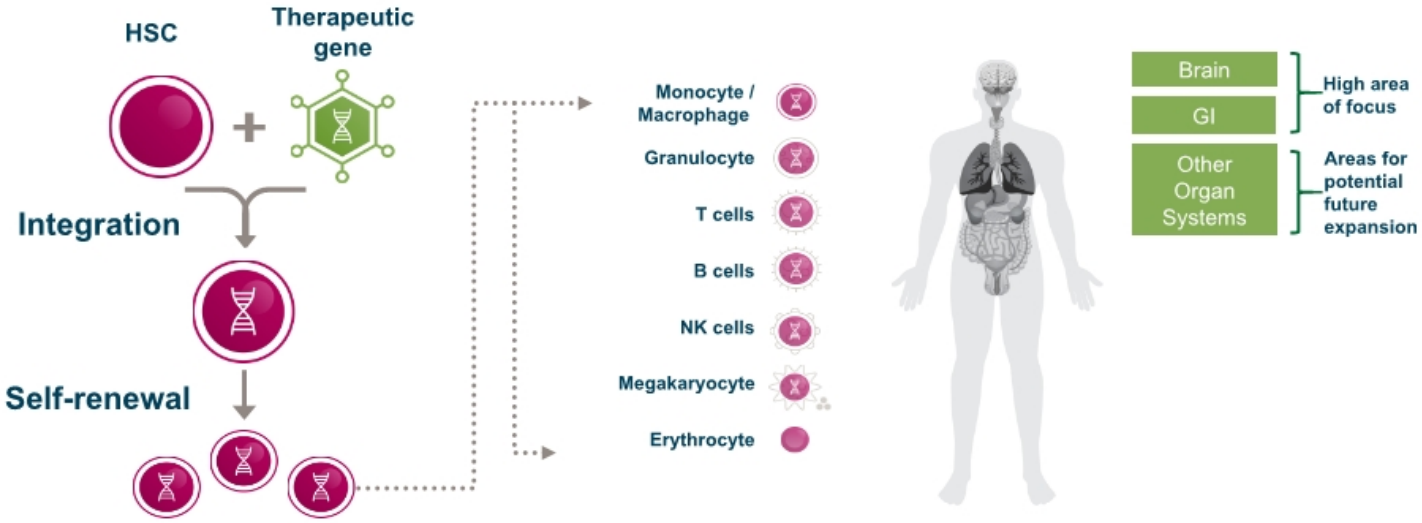
Orchard therapeutics

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 constitute forward-looking statements and may include, but are not limited to, the Company's expectations 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 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 Libmeldy and the Company's product candidates; and (xi) expected financial performance and financial condition. 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 Orchard'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; and, the severity of the 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 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 4, 2021, 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.

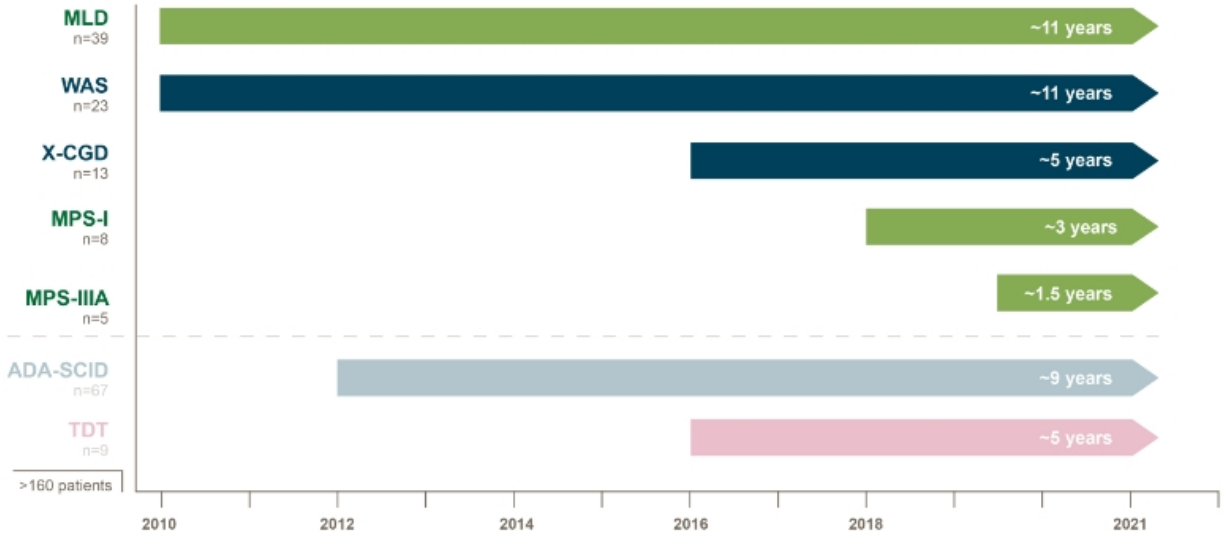
HSC Gene Therapy Offers a Highly Differentiated Approach



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

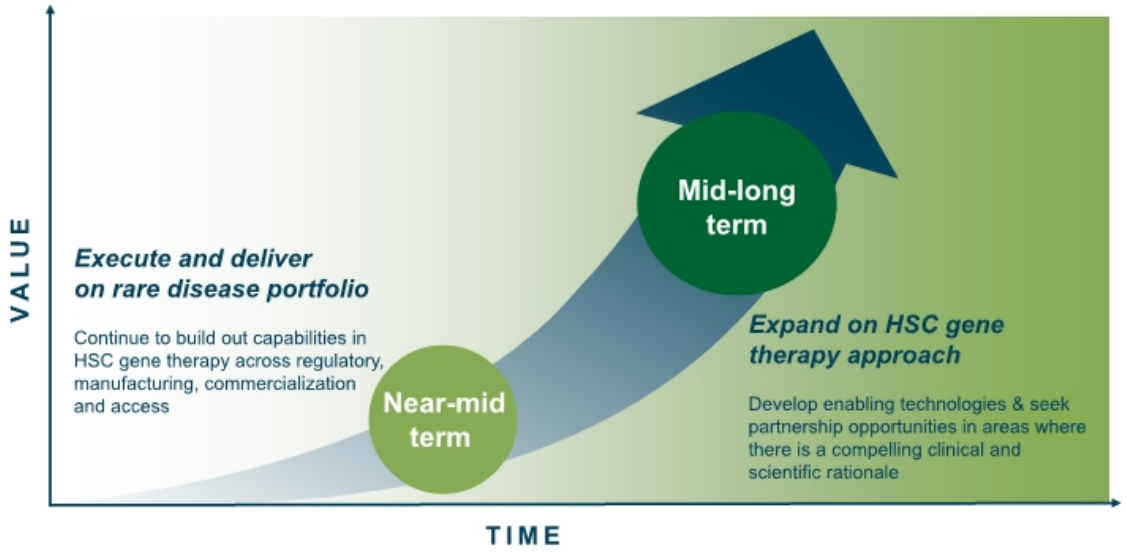
Durability of Response Demonstrated via Longest Patient Follow-up with Orchard's HSC Gene Therapy



- 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 February 2021 and comprises all patients treated with CD34+ hematopoietic stem cells transduced *ex vivo* with vector of interest, inclusive of current and former programs.

Orchard therapeutics

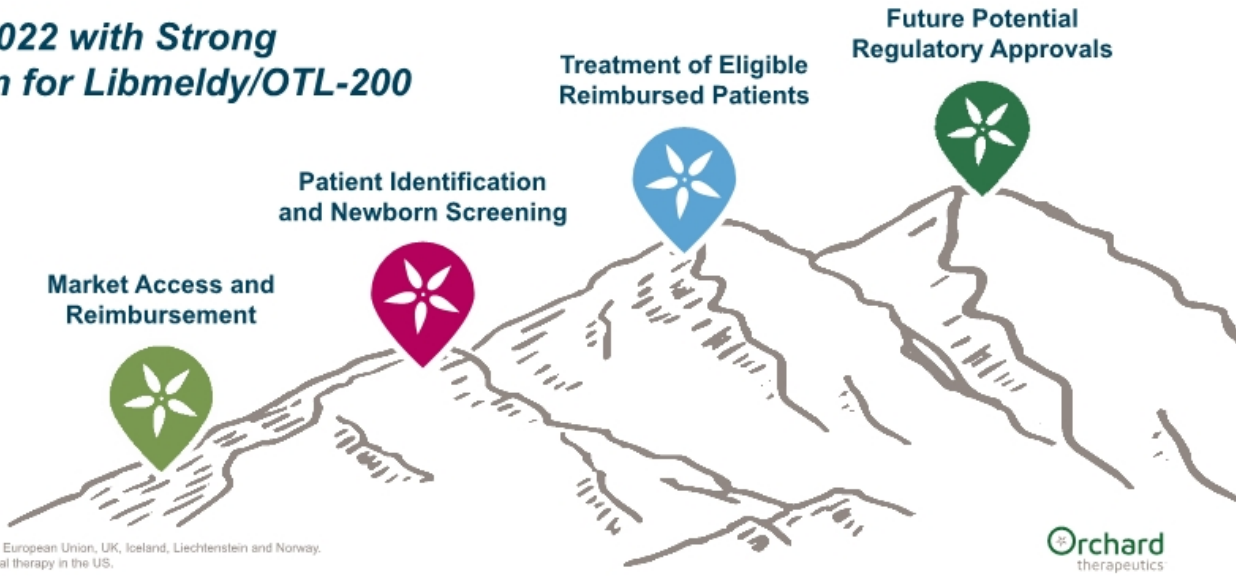
Accelerating Long-term Growth and Value Creation By Expanding into Other Neurodegenerative and Immunological Diseases



Orchard therapeutics

Reaching New Heights

Entering 2022 with Strong Momentum for Libmeldy/OTL-200



Libmeldy is approved in the European Union, UK, Iceland, Liechtenstein and Norway.
OTL-200 is an investigational therapy in the US.

Orchard therapeutics

European HTA and Reimbursement Discussions Progressing Well

Broad Recognition of Libmeldy's Clinical Impact

Achieved highest possible therapeutic benefit rating in pre-symptomatic patients in Germany

Granted approval for reimbursed early access program in France

Ongoing collaboration with NICE and NHS England in advance of Final Evaluation Determination

Approved to treat patients travelling to Italy from countries outside Europe; negotiating final pricing & reimbursement for native patients

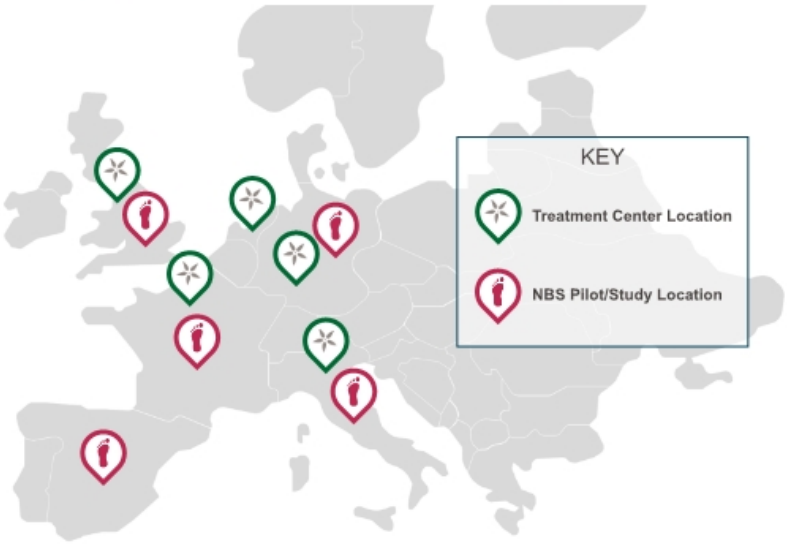
Orchard therapeutics

Utilizing Our Commercial Infrastructure to Identify, Treat and Secure Reimbursement for Eligible Patients in Europe

2 eligible patients in process of reimbursed treatment

4 centers treatment ready

5 Newborn screening (NBS) pilots/studies launched or planned



Orchard therapeutics

OTL-200 (MLD): Advancing U.S. Regulatory Discussions

BLA expected late 2022 / early 2023

- ✓ RMAT meeting with confirmation of expected clinical package
- ✓ Productive Type B CMC meeting
- ✓ Clarity on manufacturing facility FDA inspection readiness
- ✓ Provided OTL-200 for U.S. investigator-initiated compassionate use INDs; Successfully released investigational drug product shipped between U.S. treatment site and EU CDMO
- ○ NEXT STEP: Pre-BLA submission meeting with U.S. FDA

Looking to New Horizons

Deliver on rare disease portfolio

Meet the need in genetic and other severe diseases

Expand HSC gene therapy approach

Orchard therapeutics

OTL-103 for WAS: Progressing Toward Regulatory Submissions in Europe and the U.S.

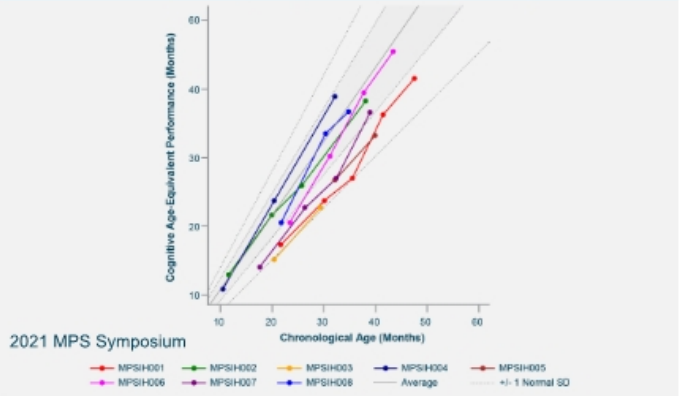
- ✓ Productive rapporteur / co-rapporteur interactions
- ○ MAA filing planned for mid-2022

- ✓ Active IND / RMAT designation
- ○ FDA interaction planned for early 2022

OTL-203 for MPS-IH: Stable Cognitive Function and Growth within the Normal Range in Proof-of-concept Study

Neuropsychological Tests over Time

Cognitive Age-Equivalent Score (Overall)



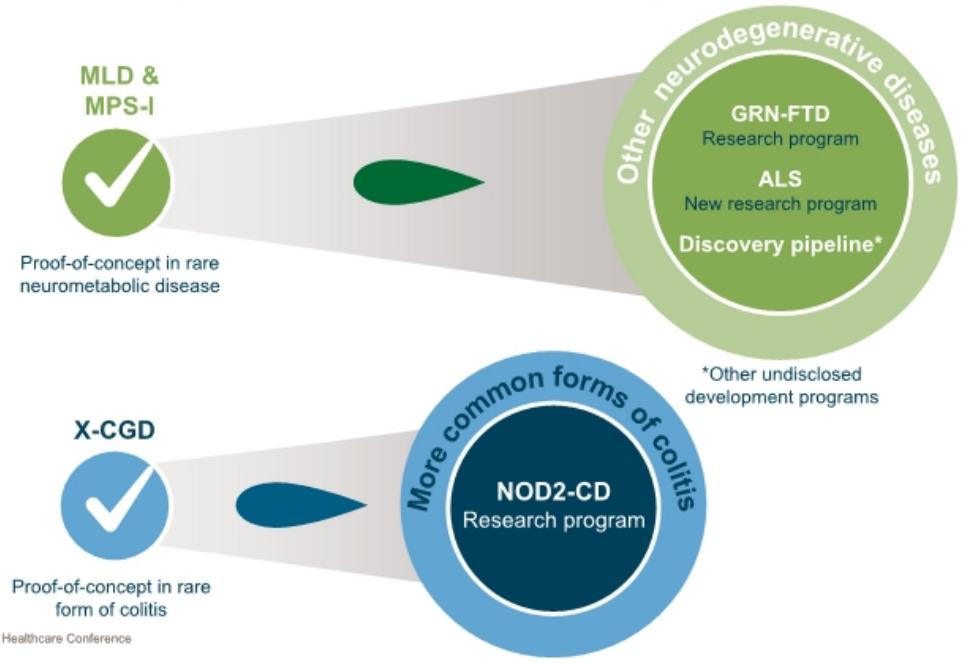
Note: SD = Standard Deviation; IQ(C) = Intelligence Quotient (Cognition); For Bayley III, the IQ(C) is the cognitive composite score as collected. For WPPSI, the IQ(C) is defined as the performance scales score. For Bayley II: Cognitive Age-Equivalent will be defined as the Mental developmental Age recorded on the CRF. For Bayley III: Cognitive Raw Scores will be compared to the tabulated values in the Bayley III manual to calculate the Cognitive Age-Equivalent. For WPPSI, Age-Equivalent = (IQ*Chronological Age)/100.

Recent Program Achievements and Next Steps

- ✓ Conducted parallel scientific advice meeting with EMA and FDA
- ✓ Proof-of-concept study results published in *New England Journal of Medicine*
- ○ Obtain necessary regulatory clearance in mid-2022 to enable global registrational study
- ○ Initiate global registrational trial by year end

Orchard therapeutics

Rare Disease Portfolio Provides Clinical Proof-of-concept in More Prevalent Neurodegenerative and Immunological Diseases



Orchard therapeutics

Orchard's Discovery and Early Research Program Highlights

Neurodegenerative disorders

- Approach leverages success of Libmeldy in **whole-brain secretion of ARSA from fully distributed microglial cells**
- Targets include GRN-FTD, ALS and other indications

Status:
Tech. development and preclinical proof-of-concept models ongoing

NOD2 Crohn's disease

- Orchard is developing OTL-104, an HSC gene therapy product targeting NOD2 mutations associated with Crohn's disease severity
- **Early preclinical data shows potential**

Status:
Preclinical proof-of-concept models ongoing

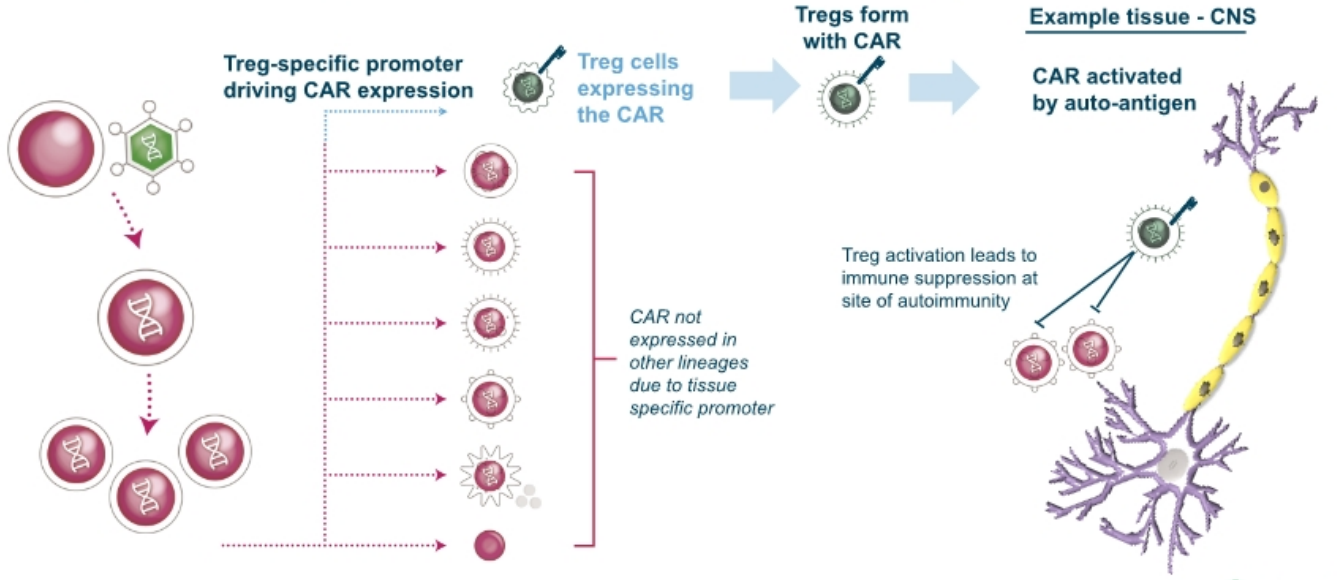
Future Applications for HSC Gene Therapy

- Two key areas to **expand HSC gene therapy platform:**
  1. Vectorized antibody platform to **deliver mAbs to specific tissues or sites**
  2. HSC CAR-Treg platform as a durable therapy for **autoimmune disorders**

Status:
Exploratory research ongoing

Orchard therapeutics

Combining the Proven Durability of HSC Gene Therapy with the Specific Suppressive Potential of CAR-Tregs



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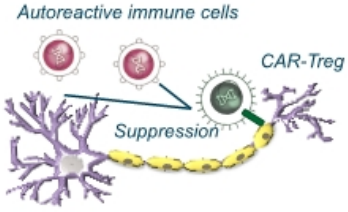
Potential Applications of the HSC CAR-Treg Technology

Multiple sclerosis

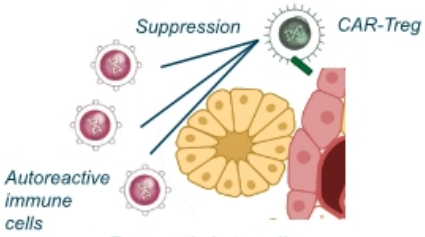
- **Identified antigen:** MOG and MBP
- **Use of HSC transplant:** Yes, 100s per year with limited efficacy
- **Unmet medical need:** High, particularly in progressive disease



Myelin sheath

Type 1 Diabetes

- **Identified antigen:** GAD65, chromogranin A, others
- **Use of HSC transplant:** Yes, but limited efficacy
- **Unmet medical need:** Many patients not reaching HbA1c goals



Pancreatic beta-cells

Rheumatoid arthritis

- **Identified antigen:** Limited, ova is one example
- **Use of HSC transplant:** Yes, but limited efficacy
- **Unmet medical need:** Significant proportion of patients non controlled on existing therapies

Synovial tissue

Image credit: Biorender

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The Journey Ahead

Roadmap for a sustainable future

Maintain strong balance sheet

Multiple near-term value-creating milestones expected

Invest for growth

Leverage HSC GT platform as engine for new indications

Utilize global infrastructure and footprint for future potential approvals and launches

Pursue partnership opportunities

Potential for disease-specific or technology driven approaches

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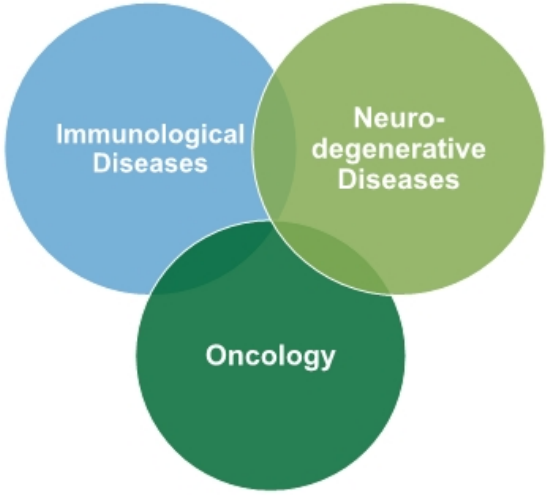
Research Platform Provides Multiple Opportunities for Business Development



Partnerships in specific diseases

- **OTL-105** for HAE partnered with Pharming
- Leveraging ongoing programs in CNS **(FTD/ALS)** and colitis **(NOD2-Crohn's)**

Partnerships built on specific technologies

- **Antigen-specific Tregs** for autoimmune diseases
- **mAb vectorization technology** to target specific tumors or other targets

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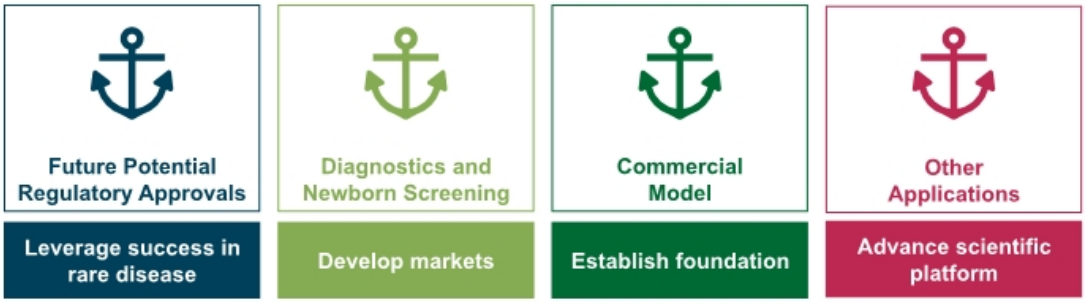
Anticipated 2022 Milestones:

A Catalyst-Rich Year Spanning All Phases of Development and Commercialization

Preclinical	Clinical	Regulatory	Commercial
Advance research programs in **GRN-FTD (OTL-204), NOD2-CD (OTL-104), HAE (OTL-105) and HSC-generated antigen-specific Tregs**	**OTL-203:** Initiate global registrational trial for MPS-IH by year end **OTL-201:** Present data from ongoing MPS-IIIA POC trial in 1H'22	**OTL-103:** MAA filing in WAS in mid-2022; FDA interaction planned in early 2022 to discuss elements of a potential BLA filing package **OTL-200:** Planned BLA submission for MLD in late 2022 / early 2023	**Libmeldy:** Reach reimbursement agreement with at least two countries in 1H'22 **Libmeldy:** Continue to broaden patient identification and newborn screening initiatives

Compelling Fundamentals Driving Near-term Value Creation and Long-term Growth



All based on a de-risked HSC GT scientific and clinical platform

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Thank you!

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