Q3 2022 Financial Results and Business Highlights

November 14, 2022

Orchard therapeutics

Forward-looking Statements

Certain information set forth in this presentation and in statements made orally during this presentation contain “forward-looking statements”. Except for statements of historical fact, information contained herein 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, 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; 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.

Non-GAAP Financial Information

Orchard has presented certain non-GAAP financial measures, including research and development costs and selling, general and administrative expenses, each excluding certain one-time charges. Management believes this non-GAAP information is useful for investors, taken in conjunction with Orchard’s GAAP financial statements, because it provides greater transparency regarding Orchard’s operating performance. Management uses these measures, among others, to assess and analyze operational results and trends and to make financial and operational decisions. Non-GAAP information is not prepared under a comprehensive set of accounting rules and should only be used to supplement your understanding of Orchard’s operating results as reported under GAAP, not as a substitute for GAAP information. In addition, these non-GAAP financial measures are unlikely to be comparable with non-GAAP information provided by other companies. Reconciliation between these non-GAAP financial measures and the most comparable GAAP financial measures is included in the financial results section of this presentation.

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Joining Today's Call

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

Braden Parker
Chief Commercial Officer

Frank Thomas
President & Chief Operating Officer

Leslie Meltzer, Ph.D.
Chief Medical Officer

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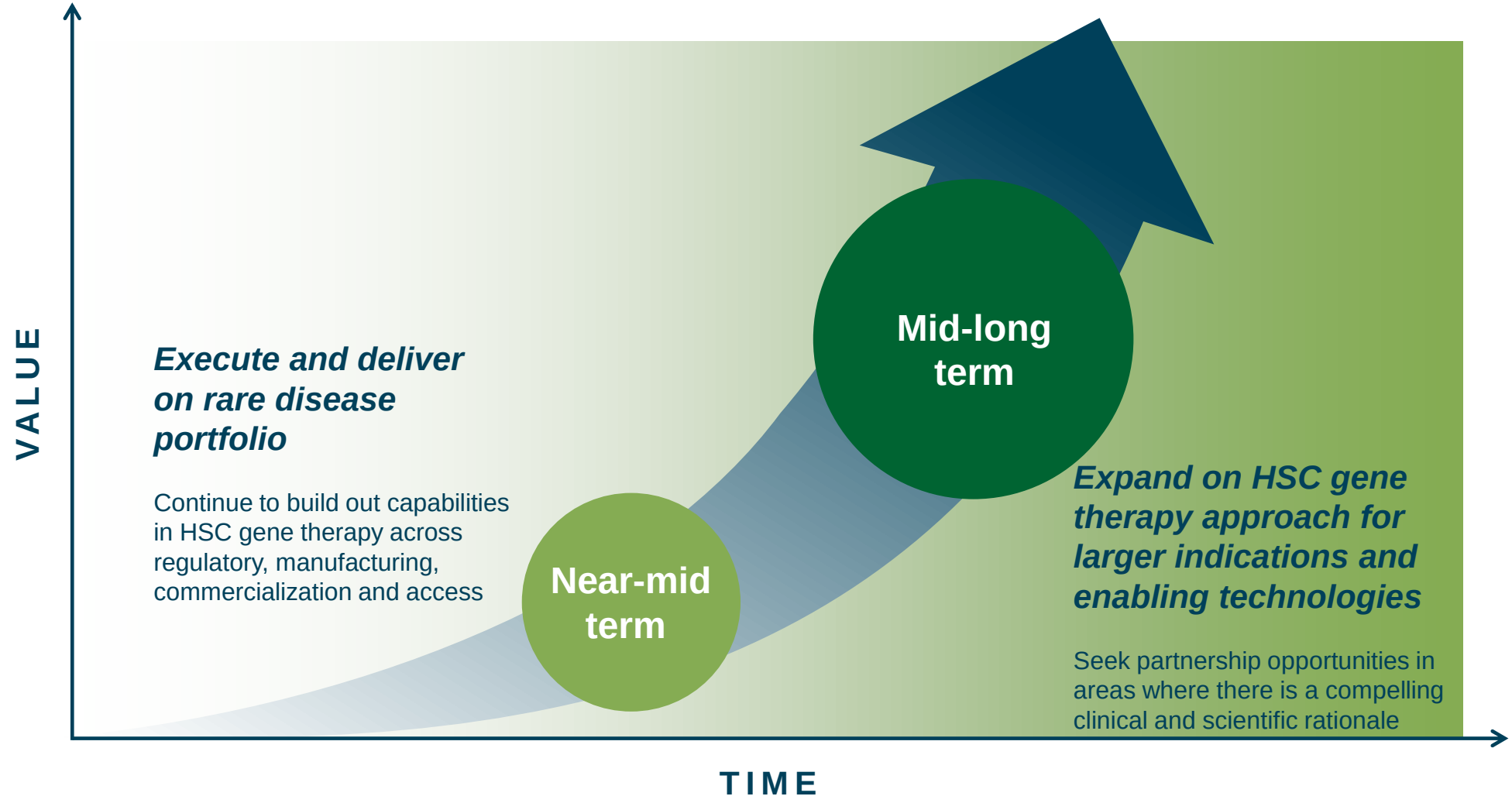
Accelerating Long-term Growth and Value Creation By Expanding into Larger Indications



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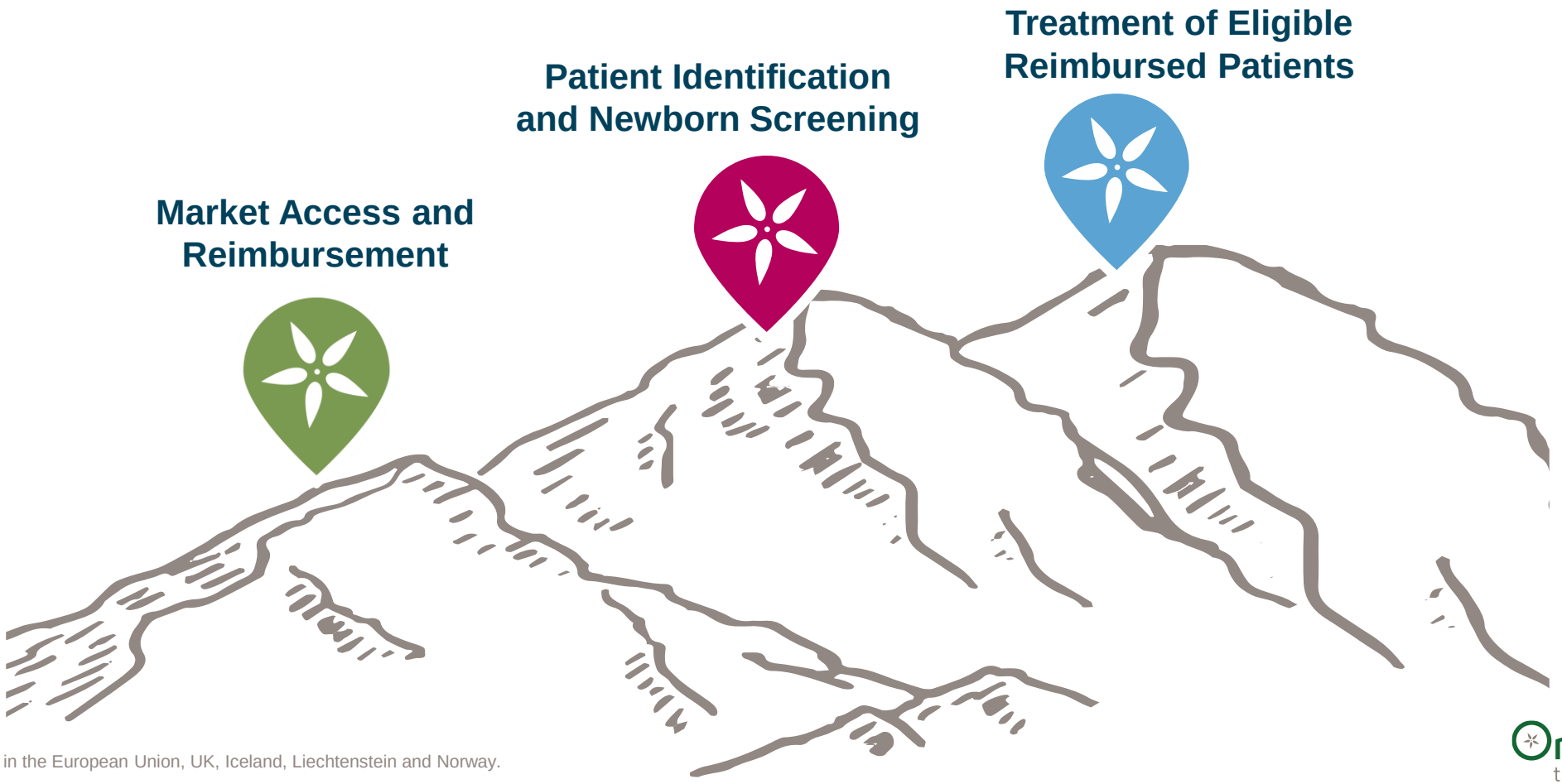
Strong Momentum for Libmeldy



Libmeldy is approved in the European Union, UK, Iceland, Liechtenstein and Norway.

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

Active dialogue around final elements of clinical + CMC packages

- ✓ **Productive clinical and CMC discussions**
- ✓ **Response to information / data requests**
- ✓ **Treatment of patients in the U.S. on compassionate use basis (with EU CDMO manufacturing)**
- ○ **Complete ongoing CMC interactions**
- ○ **Hold Type B meeting in early 2023 to discuss elements of clinical package**

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Synergies for Next in Line MPS-IH Program

Libmeldy Platform Synergies

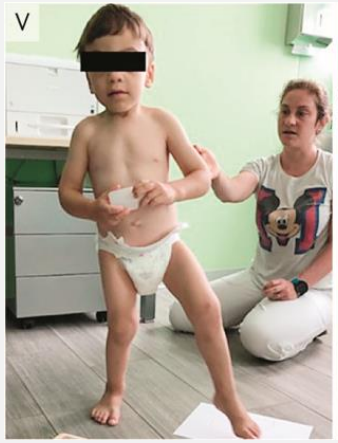
- Manufacturing, distribution, supply chain
- Regulatory learnings
- Treatment sites and referral network

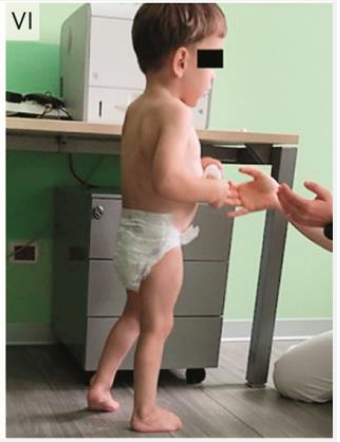
MPS-IH

- 1:100,000 live births; NBS established in some geographies, incl. U.S.
- Current SOC: HSCT and/or ERT as a bridging or chronic therapy

Before Gene Therapy

After Gene Therapy





OTL-203 Program Status

- POC data published in NEJM
- Conducted parallel scientific advice meeting with EMA and FDA
- Initiate a global registrational study by year-end 2023

SD = Standard Deviation; IQ(C) = Intelligence Quotient (Cognition); See 2021 MPS Symposium for further details

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OTL-201 Abstract for MPS-IIIA Accepted for Oral Presentation at ASH

- Five patient POC study with partners at the University of Manchester and Royal Manchester Children's Hospital
- Robust, sustained hematological engraftment
- Supraphysiological levels of SGSH enzyme + normalization of heparan sulphate

First neurocognitive data to be presented at ASH

Title: "Biochemical Engraftment and Clinical Outcomes Following Ex-Vivo Autologous Stem Cell Gene Therapy for Mucopolysaccharidosis Type IIIA"

Date/Time: Monday, December 12, 2022, at 10:45 a.m. CST

Presenter: Rob Wynn

IR event: Monday, December 12, 2022, at 5:00 p.m. EST

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Commercializing Libmeldy

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Tremendous Momentum with Libmeldy Commercial Launch in 2022

Qualified Treatment Centers

4 out of 5 treatment centers have treated a commercial patient

Market Access & Reimbursement

Reimbursement secured for all eligible MLD children

UK

Italy

Germany

- **France:** Reimbursed early access program renewed

Launch Expansion

Expansion activities underway

Beneluxa consortia includes Belgium, the Netherlands, Luxembourg and Austria
FINOSE collaboration includes Finland, Norway and Sweden

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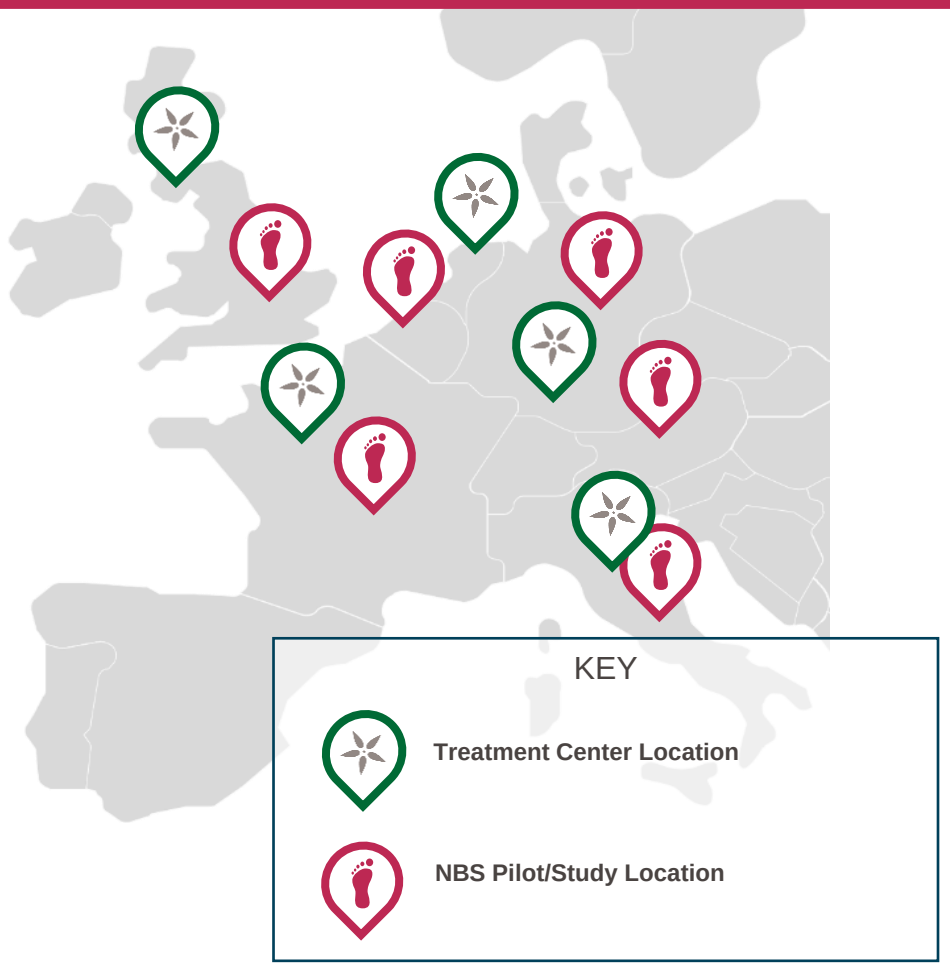
Implementing Newborn Screening for MLD

Treatment Centers and Newborn Screening (NBS)



Some countries have more than one NBS site

First confirmed case of MLD identified from ARCHIMEDlife study

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Q3 Financials and Upcoming Milestones

Key Financial Highlights with Cash Runway into Q2 2024

(amounts in millions)	Three Months Ended September 30	
	2022	**2021**
Product revenue, net	*$5.4M*	*$0.7M*
Libmeldy product sales	$4.8M	-
Strimvelis product sales	$0.6M	$0.7M
Collaboration revenue	$0.4M	$0.5M
Total revenues	*$5.8M*	*$1.2M*
Costs and operating expenses:		
Cost of product sales	$1.6M	$0.2M
Research and development	$18.1M	$20.8M
Selling, general and administrative	$11.5M	$13.0M
Total costs and operating expenses	*$31.2M*	*$34.1M*
Loss from operations	*$25.5M*	*$32.9M*

Balance Sheet (*in millions*)	**As of 9/30/22**
Cash & investments	$146.6M
Long-term debt (notional amount)	$33.0M

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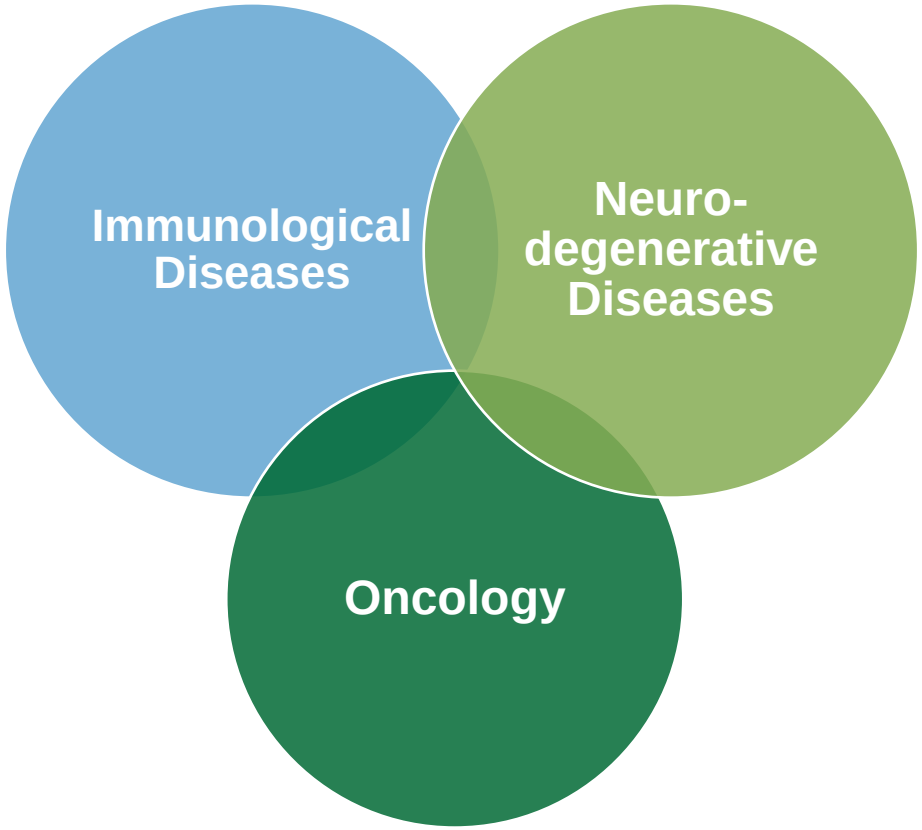
Our Platform Provides Multiple Opportunities for Business Development



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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Runway Covers Multiple Anticipated Milestones into 2024

Spanning Commercialization and All Phases of Development

1H'22

Commercial

Libmeldy: Reach reimbursement agreement with at least two countries

- ✓ UK
- ✓ Italy
- ✓ Germany

2H'22

Development

OTL-201: Report data from ongoing MPS-IIIA POC trial at ASH

2023

Regulatory

Pre-clinical

OTL-200: Clinical Type B meeting w/ FDA (early 2023)

OTL-104: Report preclinical POC data for NOD2-CD (early 2023)

OTL-203: Initiate global registrational trial for MPS-IH in 2023

2024

OTL-104: Submit IND filing in NOD2-CD

Advance preclinical pipeline (**OTL-105** for **HAE**, **OTL-204** for **GRN-FTD** & **Tregs**)

$147M cash & investments / runway into Q2 2024

Libmeldy commercialization + revenue generation

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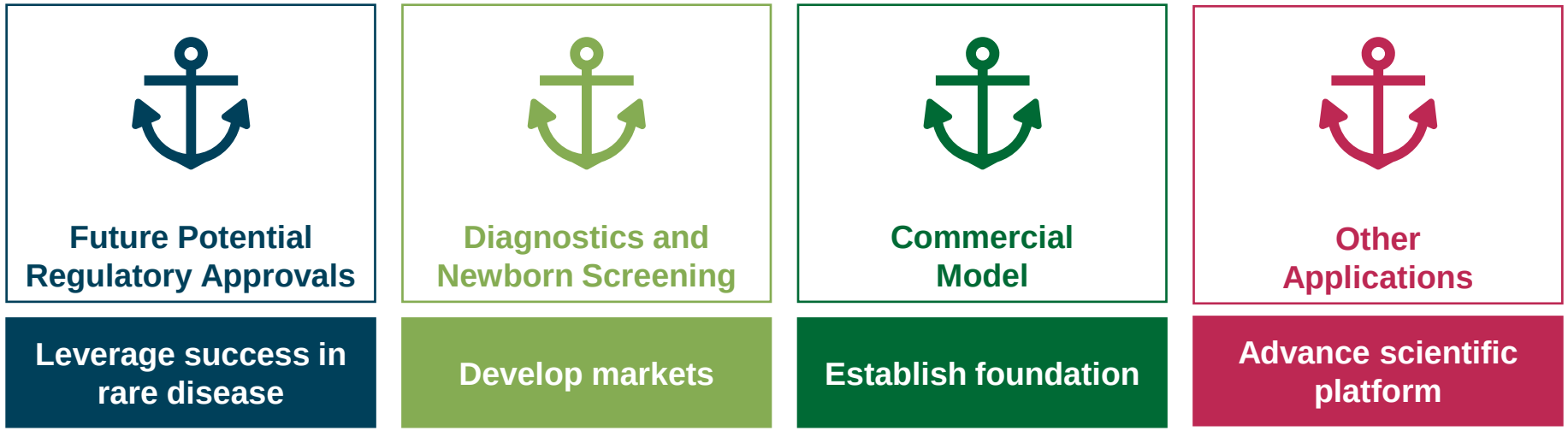
Compelling Fundamentals Driving Near-term Value Creation and Long-term Growth



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

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