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

Forward-looking Statements

Certain information set forth in this presentation and in statements made orally during this presentation contain “forward-looking statements”. Such forward-looking statements may be identified by words such as “estimated,” “anticipates,” “believes,” and “expects,” or similar expressions, which are intended to identify forward-looking statements. Forward-looking statements include express or implied statements relating to, among other things: Orchard Therapeutics plc’s (“Orchard’s” or the “Company’s”) business strategy and goals; the therapeutic potential of Orchard’s products and product candidates; Orchard’s expectations regarding the timing of regulatory submissions for approval of its product candidates, including the timing of a Biologics License Application (BLA) submission for OTL-200; the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates; the timing of the expected registrational study for OTL-203 for MPS-IH; the timing of announcement of clinical data for its product candidates, and the likelihood that such data will be positive and support further clinical development and regulatory approval of these product candidates; the likelihood of approval of Orchard’s product candidates by the applicable regulatory authorities; Orchard’s expectations regarding future revenue and expenses; and Orchard’s financial condition and cash runway.

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 a BLA submission for OTL-200 could be delayed; the risk that the expected BLA submission for OTL-200 may not be approved; the risk that Orchard’s future revenues could be less than expected, which could result if Orchard is unable to identify patients, secure reimbursed treatment in additional jurisdictions, or if OTL-200’s approval and commercialization in the U.S. takes longer than expected, among other ways; the risk that Orchard’s future expenses could be higher than expected; 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 risk that the ongoing COVID-19 pandemic, the war in Ukraine and other global macroeconomic and geopolitical developments could affect Orchard’s business; and the risk that the market opportunity for OTL-200 and our other product candidates may be lower than expected or that Orchard may be unable to identify patients for its products on a consistent basis. 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 (the “SEC”), as well as subsequent filings and reports filed with the SEC. The forward-looking statements contained in this presentation and in statements made orally during this presentation 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.

The estimates of revenue and expenses for the three and twelve months ended December 31, 2022 and of cash and investments as of December 31, 2022 are preliminary in nature and unaudited and do not present all information necessary for an understanding of Orchard's financial condition as of December 31, 2022 and its results of operations for the three or twelve months ended December 31, 2022.

Use of Non-GAAP Financial Measures

Orchard has presented certain non-GAAP financial measures in this presentation, including quarterly expenses that exclude certain one-time charges. Management believes this non-GAAP information is useful to investors, 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 alongside such non-GAAP information.

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Strong Operational Execution to Start 2023 Highlighted By Path to BLA Submission for OTL-200

Libmeldy EU coverage expanding further with reimbursed access in Sweden

3 genetically confirmed cases of MLD with 96,000 newborns screened globally

Constructive Type B FDA meeting on OTL-200 clinical package

Pre-BLA meeting scheduled for Q2 with potential mid-2023 submission

U.S. IND application for OTL-203 in MPS-IH cleared by the FDA

Growing revenues and ongoing expense management support sustainable business model

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Building Global Momentum for Libmeldy Commercial Potential

Commercial Activities

1) Access and treatment delivery
2) Reimbursement
3) Newborn screening to drive patient identification

Staged Areas of Focus

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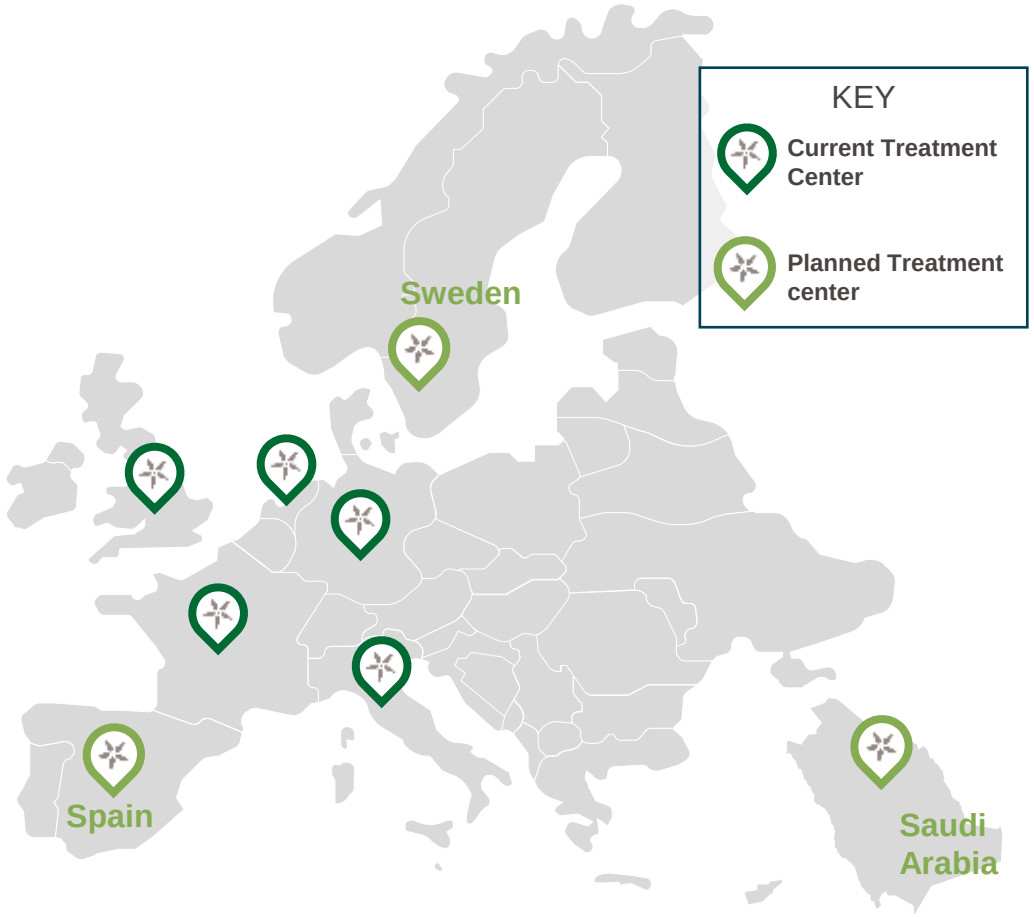
Expanding Reimbursed Access Throughout Europe

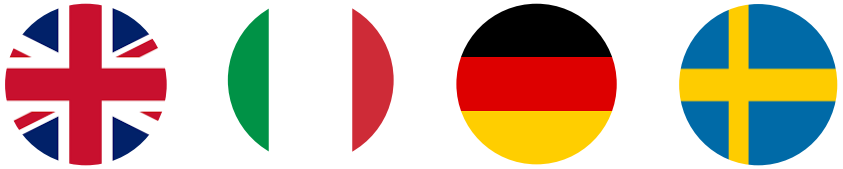
Access



Reimbursement

Secured for all eligible MLD children

UK | Italy | Germany | Sweden



Secure reimbursed treatment in at least 1 additional European country in 2023

France: Reimbursed early access program secured

Treatment abroad: patient from the Middle East

Cross border (S2) pathway: via Eastern European country

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Implementing Newborn Screening to Identify MLD Patients

Newborn Screening Pilot Studies

Three confirmed cases of MLD now identified

96,000 babies screened to date

6 studies actively screening newborns

Expanding newborn screening activities throughout Europe, the U.S. and the Middle East in 2023

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OTL-200 Pre-BLA Meeting Scheduled for Q2 with Potential for Mid-2023 Submission

- Constructive Type B FDA meeting on OTL-200 clinical package in early 2023

Target dates assume successful multidisciplinary pre-BLA meeting and priority review

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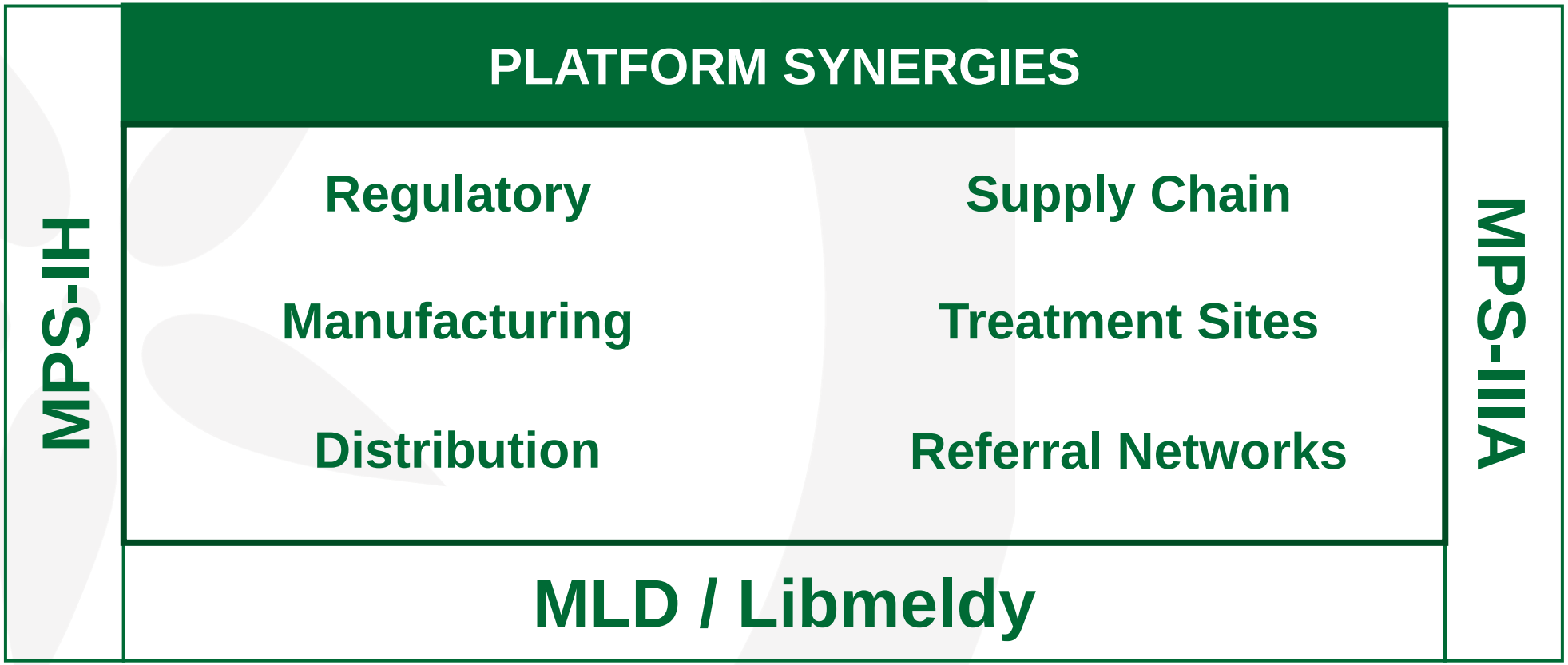
Significant Platform Synergies That Can be Leveraged Across Neurometabolic Pipeline



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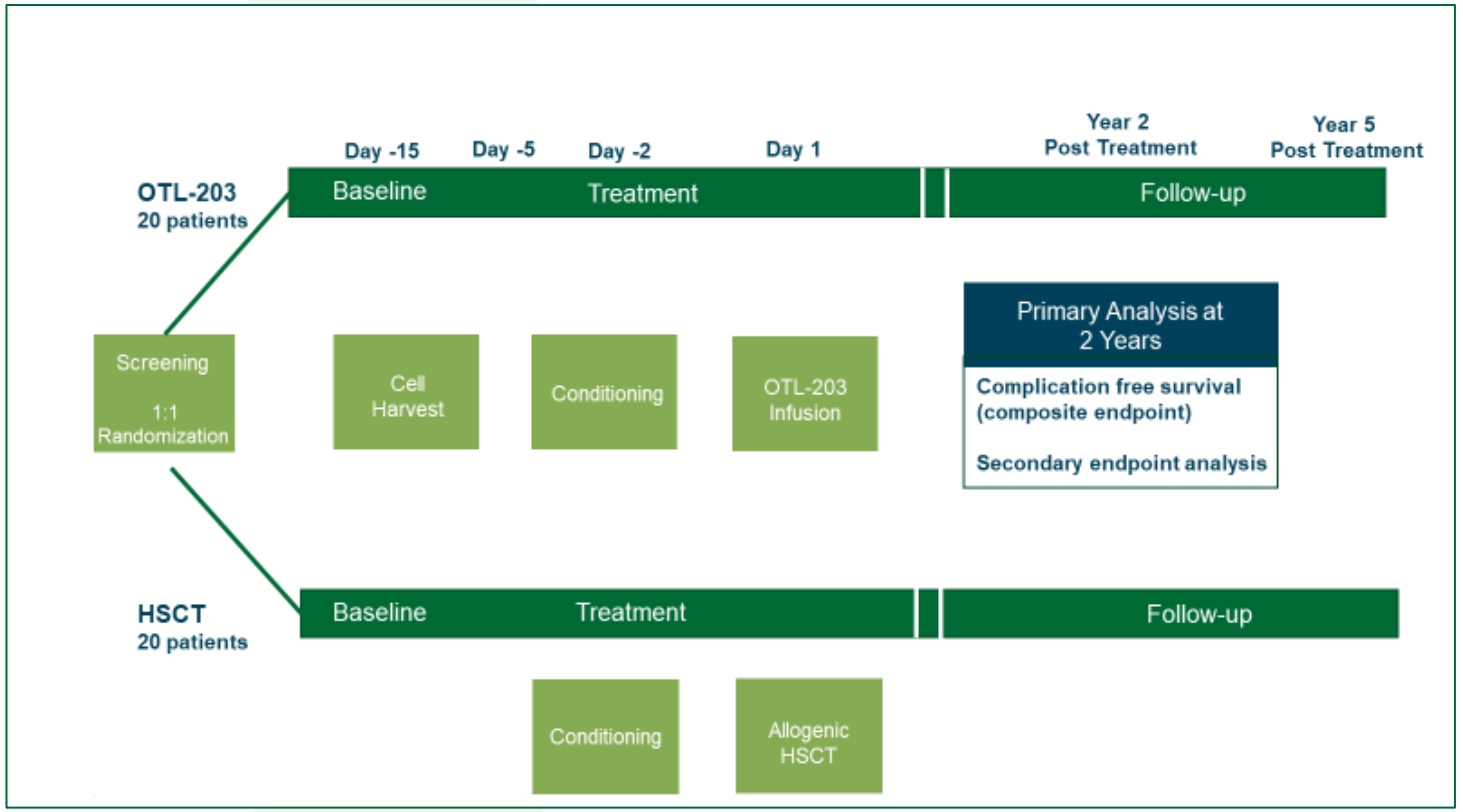
OTL-203 (MPS-IH) Moving into a Pivotal Trial in 2H 2023

- Randomized controlled trial vs. HSCT (standard of care)
- 40 patients
- 2-year primary analysis
- Composite endpoint
- Up to 6 U.S. / EU sites



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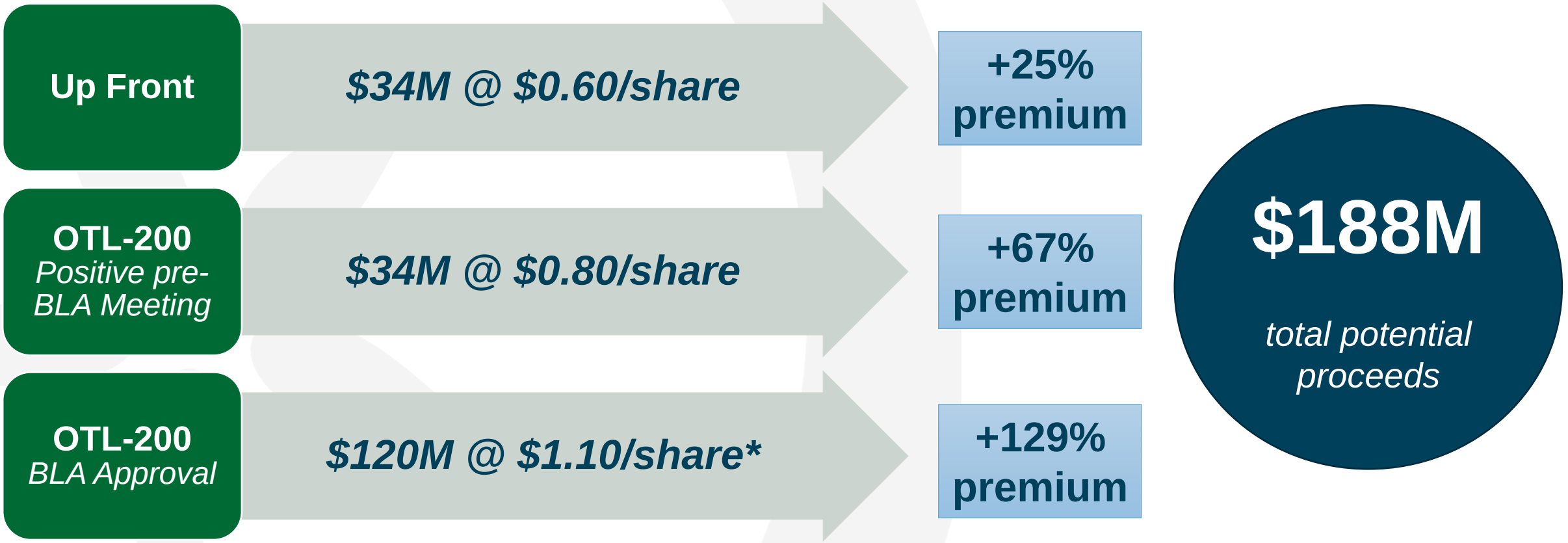
Up to $188M Strategic Financing to Fuel Long-Term Sustainability



* Warrants exercisable upon FDA approval. Price adjusts to $0.95/share if approval occurs after 2024

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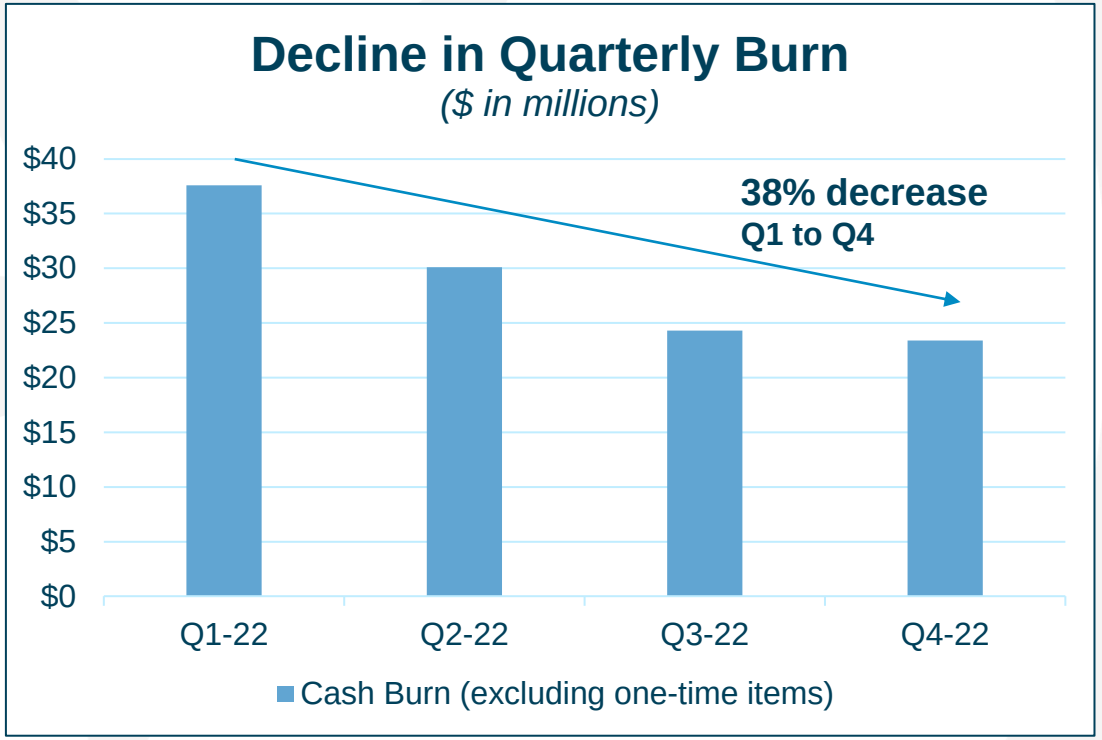
Prioritizing Expense Management, Commercialization and Development of Pipeline to Generate Value



- Annual burn rate expected to continue declining in 2023 vs. 2022
- Anticipated annual increase in Libmeldy product sales
- Continued savings realized from 2022 restructuring
- Ongoing management of operating expenses

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Q4 Key Financial Highlights

(amounts in millions)	Three Months Ended December 31	
	2022	**2021**
Product revenue, net	*$6.4M*	*$0.0M*
Libmeldy product sales	$5.8M	-
Strimvelis product sales	$0.6M	$0.0M
Collaboration revenue	$0.6M	$0.5M
Total revenues	*$7.0M*	*$0.5M*
Costs and operating expenses:		
Cost of product sales	$2.4M	$0.0M
Research and development	$25.5M	$23.3M
Selling, general and administrative	$10.6M	$13.6M
Total costs and operating expenses	*$38.6M*	*$36.9M*
Loss from operations	*$31.6M*	*$36.4M*

Balance Sheet (*in millions*)	**As of 12/31/22**
Cash & investments	$143.8M
Long-term debt (notional amount)	$32.4M

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Executing Potential Regulatory, Clinical and Commercial Milestones

Cash Position, Including Upfront Financing Proceeds, Supports Runway into 2025

Libmeldy - Commercial

Secure reimbursed treatment in at least two additional European markets (✓ Sweden)

Establish qualified treatment centers in Sweden, Spain & Saudi Arabia

Pursue additional launch expansion opportunities

Regulatory

✓ **OTL-200:** Clinical Type B meeting w/ FDA for MLD (early 2023)

OTL-200: pre-BLA meeting (Q2 2023)

OTL-200: BLA submission (potentially mid-2023)

Development

OTL-203: Initiate global registrational trial for MPS-IH in 2H 2023

OTL-201: Report additional biochemical / clinical data from ongoing MPS-IIIA PoC study in 2023

Preclinical

OTL-104: Report preclinical PoC data for NOD2-CD (1H 2023)

OTL-104: Initiate IND-enabling activities ahead of 2024 planned IND submission

~$178M in pro forma cash & investments as of YE 2022

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

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