Orchard Therapeutics Extends Runway into 2024, Focusing HSC Gene Therapy Platform Exclusively on Severe Neurometabolic Diseases and Research Platform

March 30, 2022

Libmeldy European launch momentum building with multiple MLD patients treated and strong recognition of value proposition; U.S. BLA filing of OTL-200 on track for late 2022 / early 2023

Broad research platform presents opportunities for larger indications and partnerships; preclinical POC data in NOD2 Crohn's disease expected by year end and IND filing planned in 2024

Plan to seek strategic alternatives for primary immunodeficiency programs, including OTL-103 in WAS

Refined portfolio and 30% proposed workforce reduction extend cash runway into 2024

BOSTON and LONDON, March 30, 2022 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced its intention to focus its hematopoietic stem cell (HSC) gene therapy platform exclusively on severe neurometabolic diseases and early research programs while also reporting its financial results for the quarter and year ended December 31, 2021. These actions are intended to extend the company's cash runway into 2024 and focus operations on the highest value programs in its portfolio.

Moving forward, Orchard will continue its investment in Libmeldy® (atidarsagene autotemcel) / OTL-200 for metachromatic leukodystrophy (MLD) to help sustain recent commercial momentum in Europe, as well as to support regulatory and future commercial activities for a potential U.S. approval and launch. The company also will continue to advance clinical development of OTL-203 for mucopolysaccharidosis type I Hurler's syndrome (MPS-IH) and OTL-201 for mucopolysaccharidosis type IIIA (MPS-IIIA). The focus on these neurometabolic programs is expected to allow Orchard to leverage the clinical validation of HSC gene therapy demonstrated with Libmeldy and capture significant commercial synergies, especially given the immense unmet needs in these diseases. Promising early-stage research programs that apply the HSC gene therapy approach in NOD2 Crohn's disease, hereditary angioedema (HAE) and progranulin mutated frontotemporal dementia (GRN-FTD) also will remain an important part of the portfolio going forward given their promise in larger indications and as a possible source of future partnerships.

"In light of our experiences and knowledge gained in this current and rapidly evolving market environment for gene therapy, our plan is to concentrate resources on programs that have the potential to make a remarkable difference to patients while also providing sustainable value to the business to enable the achievement our long-term vision," said Bobby Gaspar, M.D., Ph.D., chief executive officer. "As launch momentum for Libmeldy continues to build in Europe and we prepare for a regulatory filing in the U.S., a focused strategy that utilizes a common infrastructure for future neurometabolic disease launches is critical to our success as a commercial gene therapy company."

Latest Key Milestones

To advance its portfolio of gene therapies for neurometabolic disorders and investigate future applications for the HSC approach, Orchard has provided an updated list of expected milestones:

- Libmeldy launch (Europe): Reach a reimbursement agreement with one additional country (in addition to the previously announced agreement with National Health Service (NHS) England) in the first half of 2022, followed by additional agreements as negotiations are completed.
- OTL-200 for MLD (U.S): Conduct a pre-Biologics License Application (BLA) meeting with U.S. Food and Drug Administration (FDA) for OTL-200 in the second half of 2022 in advance of a BLA submission timeline of late 2022 to early 2023.
- OTL-203 for MPS-IH: Obtain the necessary Investigational New Drug application (IND) clearance in mid-2022 to enable the initiation of the OTL-203 registrational study in MPS-IH by year end 2022.
- OTL-201 for MPS-IIIA: Report clinical data, including early clinical outcomes of cognitive function, from the OTL-201 proof-of-concept (POC) trial by year end 2022.
- Research programs: Report preclinical POC data for the OTL-104 program in NOD2 Crohn's disease (NOD2-CD) by year end 2022 and file an IND in 2024. Continue to advance the OTL-105 program in HAE, OTL-204 program for GRN-FTD and work in HSC-generated antigen-specific Tregs.

Libmeldy Recent Highlights

- Commercial progress:
  - In February, Orchard announced it reached an agreement with the NHS that enables access to Libmeldy for all children with MLD in England and Wales who fall within the scope of the European marketing authorization. Libmeldy is the first-ever lentiviral HSC gene therapy approved for reimbursement by NHS England.
  - In addition, the company announced the commercially reimbursed treatment of the first three Libmeldy patients

from Europe and the Middle East. The link to the full release describing the above commercial updates is available here.

- Data publication:
  - In January, *The Lancet* published long-term clinical outcomes evaluating the safety and efficacy of Libmeldy for the treatment of early-onset MLD. The link to the full release is available here.

Portfolio and Organizational Updates

To support the company's refined strategic focus and provide runway extension into 2024, Orchard intends to discontinue its investment in and seek alternatives for its programs in rare primary immune deficiencies. These include OTL-103 for the treatment of Wiskott-Aldrich syndrome (WAS), OTL-102 for X-linked chronic granulomatous disease (X-CGD) and Strimvelis®, a gammaretroviral vector-based gene therapy approved in Europe for adenosine deaminase severe combined immunodeficiency (ADA-SCID).

Regarding the regulatory status of the OTL-103 program in the U.S., Orchard recently received written feedback from the FDA. The company believes the path to a potential BLA filing may require additional time and further investment.

Gaspar continued, "We recognize the significant need that persists for many patients suffering from these rare diseases of the immune system, and we sympathize with the individuals, families and healthcare providers affected by these announcements, as well as our clinical partners and colleagues who worked so hard to advance these programs. These therapies have shown the potential for significant benefit for many patients treated in the clinical studies and we will continue to look for alternative ways to advance them, which could include commercial partnerships."

As a result of these updates, the company has proposed to reduce its current workforce by approximately 30%, which will result in a restructuring charge in 2022. Collectively, the actions announced today are expected to extend the company's existing cash runway into 2024.

Fourth Quarter 2021 Financial Results

Research and development expenses were $23.3 million for the three months ended December 31, 2021, compared to $22.6 million in the same period in 2020. R&D expenses include the costs of clinical trials and preclinical work on the company's portfolio of investigational gene therapies, as well as costs related to regulatory, manufacturing, license fees and milestone payments under the company's agreements with third parties, and personnel costs to support these activities. The company expects R&D expenses to decline beginning in the second quarter of 2022 due to the portfolio updates and workforce reduction announced today as well as the completion of activities to support the OTL-200 BLA submission.

Selling, general and administrative expenses were $13.6 million for the three months ended December 31, 2021, compared to $16.2 million in the same period in 2020. The decline from 2020 resulted primarily from lower cash and share-based personnel costs to align with the current filing timelines and commercialization plans. In 2022, the company expects SG&A expenses to decline from 2021 due to the workforce reduction announced today, partially offset by increasing commercialization expenses to support Libmeldy, including preparations for a potential U.S. launch in 2023.

Net loss was $36.4 million for the three months ended December 31, 2021, compared to $ 33.6 million in the same period in 2020. The company had approximately 125.7 million ordinary shares outstanding as of December 31, 2021.

Cash, cash equivalents and investments as of December 31, 2021, were approximately $220.1 million, with $33.0 million of debt outstanding, compared to $191.9 million and $25.0 million of debt outstanding as of December 31, 2020. Following the actions announced today, the company now expects that its existing cash, cash equivalents and investments will fund its anticipated operating and capital expenditure requirements into 2024.

Conference Call & Webcast Information

Orchard will host a conference call and live webcast with slides today at 8:00 a.m. ET to discuss the updates to its business strategy. The conference call will be broadcast live in listen-only mode under "News & Events" in the "Investors & Media" section of the company's website at www.orchard-tx.com, and a replay will be archived on the Orchard website following the presentation. To ask a question, please dial (866) 987-6504 (U.S. domestic) or +1 (602) 563-8620 (international) and refer to conference ID 9445456. Please dial in at least 15 minutes in advance to ensure a timely connection to the call.

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 of Libmeldy, 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 U.S.

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

About Orchard's Investigational Primary Immune Deficiency Portfolio

Primary immune deficiencies (PIDs) are a group of rare, genetic disorders in which the immune system does not function properly, leading to frequent

infections and other disease manifestations that can be life-threatening. Orchard's PID portfolio includes HSC gene therapies in development for the treatment of Wiskott Aldrich syndrome (WAS), X-linked chronic granulomatous disease (X-CGD), and Adenosine deaminase severe combined immunodeficiency (ADA-SCID). More than 100 PID patients have received one of Orchard's investigational gene therapy products, with 11 years follow-up in the earliest treated patients. The majority of patients experienced favorable clinical outcomes and there was no evidence of monoclonal expansion, leukoproliferative complications or emergence of replication competent lentivirus.

About Strimvelis®

Strimvelis *(autologous CD34$^+$ enriched cell fraction that contains CD34$^+$ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence)* is a gammaretroviral vector-based gene therapy approved by the European Medicines Agency (EMA) in 2016. It was the first *ex vivo* autologous gene therapy approved by the EMA. Strimvelis has not been approved by the U.S. Food and Drug Administration (FDA).

Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)- matched related stem cell donor is available. Strimvelis is intended solely for autologous use and must be given in a specialized hospital by a doctor who is experienced in treating patients with ADA-SCID and in using this type of medicine.

Serious adverse reactions include autoimmunity (*e.g.*, autoimmune hemolytic anemia, autoimmune aplastic anemia, autoimmune hepatitis, autoimmune thrombocytopenia and Guillain-Barré syndrome). The most commonly reported adverse reaction was pyrexia.

For more information about Strimvelis, please see the EU Summary of Product Characteristics available on the EMA website.

About Orchard Therapeutics

At Orchard Therapeutics, our vision is to end the devastation caused by genetic and other severe diseases. We aim to do this by discovering, developing and commercializing new treatments that tap into the curative potential of hematopoietic stem cell (HSC) gene therapy. In this approach, a patient's own blood stem cells are genetically modified outside of the body and then reinserted, with the goal of correcting the underlying cause of disease in a single treatment.

In 2018, the company acquired GSK's rare disease gene therapy portfolio, which originated from a pioneering collaboration between GSK and the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy. Today, Orchard is advancing a pipeline spanning pre-clinical, clinical and commercial stage HSC gene therapies designed to address serious diseases where the burden is immense for patients, families and society and current treatment options are limited or do not exist.

Orchard has its global headquarters in London and U.S. headquarters in Boston. For more information, please visit www.orchard-tx.com, and follow us on Twitter and LinkedIn.

Availability of Other Information About Orchard Therapeutics

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.com/orchard_tx and www.linkedin.com/company/orchard-therapeutics), 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. Such forward-looking statements may be identified by words such as "anticipates," "believes," "expects," "plans," "intends," "projects," and "future" or similar expressions that are intended to identify forward-looking statements. Forward-looking statements include express or implied statements relating to, among other things, Orchard's business strategy and goals, the therapeutic potential of Orchard's products and product candidates, including the products and product candidates referred to in this release, Orchard's expectations regarding the timing of regulatory submissions for approval of its product candidates, including the product candidates referred to in this release, the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates, the timing of announcement of clinical data for its product candidates, 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 such product candidates by the applicable regulatory authorities, the size of the potential markets for Libmeldy and Orchard's other product candidates, the expected benefits to Orchard's business as a result of the organizational updates referred to in this release, the adequacy of the company's manufacturing capacity and plans for future investment, and the company's financial condition and cash runway into 2024. 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: that the cost of discontinuing or partnering programs may be higher than expected; the risk that Orchard will not realize the anticipated benefits of its new strategic plan or the expected cash savings; 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 risk of delays in Orchard's ability to commercialize its product candidates, if approved; the risk that the ongoing and evolving COVID-19 pandemic could affect the company's business; and the risk that the market opportunity for Libmeldy and its other product candidates may be lower than estimated. Given these uncertainties, the reader is advised not to place any undue reliance on such forward-looking statements.

Other risks and uncertainties faced by Orchard include those identified under the heading "Risk Factors" in Orchard's most recent annual or quarterly

report filed with the U.S. Securities and Exchange Commission (SEC), as well as subsequent filings and reports filed with the SEC. The forward-looking statements contained in this press release reflect Orchard's views as of the date hereof, and Orchard does not assume and specifically disclaims any obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

Condensed Consolidated Statements of Operations Data
(In thousands, except share and per share data)
(Unaudited)

	Three months ended December 31,	
	2021	**2020**
Collaboration revenue	$ 483	$ —
Total revenues	483	—
Costs and operating expenses:		
Research and development	23,346	22,648
Selling, general and administrative	13,552	16,226
Total costs and operating expenses	36,898	38,874
Loss from operations	(36,415)	(38,874)
Other income (expense):		
Interest income	63	279
Interest expense	(683)	(575)
Other income (expense), net	811	5,635
Total other income (expense), net	191	5,339
Net loss before income tax	(36,224)	(33,535)
Income tax (expense) benefit	(125)	(85)
Net loss	(36,349)	(33,620)
Net loss per share, basic and diluted	$ (0.29)	$ (0.34)
Weighted average shares outstanding, basic and diluted	127,519,427	99,957,965

Condensed Consolidated Balance Sheet Data
(in thousands)
(Unaudited)

	December 31,	December 31,
	2021	**2020**
Assets		
Current assets:		
Cash and cash equivalents	$ 55,912	$ 55,135
Marketable securities	164,195	136,813
Trade receivables	1,480	878
Prepaid expenses and other current assets	23,011	13,365
Research and development tax credit receivable, current	30,723	17,344
Total current assets	275,321	223,535
Non-current assets:		
Operating lease right-of-use assets	24,316	29,815
Property and equipment, net	4,767	4,781
Intangible assets, net	4,149	3,076
Other long-term assets	13,856	19,730
Total non-current assets	47,088	57,402
Total assets	$ 322,409	$ 280,937
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 10,008	$ 8,823
Accrued expenses and other current liabilities	24,318	28,943
Deferred revenue	346	—
Operating lease liabilities	7,335	8,934
Notes payable, current	786	4,861
Total current liabilities	42,793	51,561
Notes payable, long-term	32,086	20,204
Deferred revenue, net of current portion	12,519	—
Operating lease liabilities, non-current	19,278	24,168

Other long-term liabilities	5,783	6,570
Total liabilities	112,459	102,503
Shareholders' equity:	209,950	178,434
Total liabilities and shareholders' equity	$ 322,409	$ 280,937

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