Orchard Therapeutics Announces Positive Clinical and Preclinical Data in Programs Targeting Neurometabolic and CNS Disorders at ASGCT

May 19, 2023

New OTL-203 proof-of-concept data demonstrate extensive metabolic correction in the skeletal system of patients with MPS-IH including normal growth rates, improvement in joint function and progressive acquisition of motor skills

Updated OTL-201 data from ongoing proof-of-concept study in MPS-IIIA patients show additional favorable neurocognitive outcomes compared to disease natural history with median follow-up of 2.5 years

First preclinical data for OTL-204 highlight ability of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers in the progranulin form of frontotemporal dementia (GRN-FTD)

Company to host conference call and webcast Tuesday, May 23 at 8:00 a.m. EDT

BOSTON and LONDON, May 19, 2023 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced multiple clinical and preclinical updates from its portfolio of investigational hematopoietic stem cell (HSC) gene therapies in neurometabolic and neurodegenerative disorders. The data are being featured in several oral presentations at the ongoing 26th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT) in Los Angeles.

“Positive data from multiple clinical and preclinical studies reinforce the ability of our HSC gene therapy platform to drive the migration of gene-corrected cells into the central nervous system and other tissues and deliver therapeutic enzymes and proteins locally to potentially correct multiple severe genetic diseases,” said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard Therapeutics. “The OTL-203 and OTL-201 programs for MPS disorders are intended to address a significant medical need given the limitations or lack of effective therapies for these conditions, and present development and commercial synergies with our neurometabolic pipeline by building on our experience with Libmeldy for metachromatic leukodystrophy. The ability of HSC gene therapy to impact the CNS is further demonstrated by our research program in a genetic subtype of FTD and highlights the potential of our platform to address larger indications.”

OTL-203 (MPS-IH) Skeletal Data Summary

Yesterday’s oral presentation showcased new skeletal data for all eight proof-of-concept trial patients with a median follow-up of 3.78 years, ranging from 3.14 to 4.58 years, compared to a median of two years reported in the November 2021 *New England Journal of Medicine* publication. As previously reported, all eight participants achieved the primary endpoint of supraphysiologic blood alpha-L-iduronidase (IDUA) activity. Growth velocity, cognition and motor function post-treatment were collected as secondary and exploratory endpoints.

At baseline, most patients presented with severe joint range of motion impairment, severe acetabular (hip) dysplasia and varying degrees of dorso-lumbar kyphosis. Treatment with OTL-203 was generally well tolerated and demonstrated extensive metabolic correction over four years after treatment. All patients showed sustained engraftment of gene-corrected cells with blood IDUA activity reaching supraphysiologic levels after treatment and normal or near-normal substrate levels maintained at last follow-up. Persistent IDUA activity and substrate reduction in the cerebrospinal fluid were also seen as of last follow-up, and all patients were able to remain off treatment with enzyme replacement therapy.

In addition:

- All patients exhibited longitudinal growth within expected reference ranges of healthy children according to age and gender, with a median height gain greater than that observed in an external cohort of HSCT patients at three years of follow-up.[i]
- A clinically measurable reduction in both sitting and standing kyphosis was observed in the majority of patients. MRI spine score showed a general stabilization in all patients with no relevant signs of progression in dorso-lumbar kyphosis, vertebrae deformity and dens alterations.
- All patients progressively acquired fine and gross motor skills.
- Improvements in joint range of motion were seen compared to pre-treatment in shoulder flexion, shoulder abduction and hip and knee extension angles as compared with an external cohort of HSCT patients.[i]

The current standard of care for MPS-IH is allogeneic hematopoietic stem cell transplant (HSCT), which does not adequately address the growth and skeletal manifestations of the disease, among other clinical outcomes. Orchard plans to initiate a global 40 patient, registrational, randomized controlled trial compared to standard of care in the second half of 2023.

“MPS-IH is complex multi-system disease that places an enormous burden on affected children and their families,” said Maria Ester Bernardo, M.D., Ph.D. head of the pediatric bone marrow transplantation unit at San Raffaele Hospital and principal investigator of the proof-of-concept study. “The current standard of care, HSCT, is associated with significant morbidity and mortality and does not adequately address some of the more severe manifestations of disease, such as growth and other skeletal issues. These data, which suggest all patients are exhibiting longitudinal growth within expected reference ranges for healthy children adjusted for age and gender, suggest HSC gene therapy has the potential to offer a transformative new treatment approach. We look forward to participating in a global, multi-center registrational trial sponsored by Orchard that will commence later this year.”

OTL-201 (MPS-IIIA) Neurocognitive Data Summary

The oral presentation tomorrow will showcase updated neurocognitive data for all five patients from the ongoing proof-of-concept study, with the median follow-up now extended to 2.5 years (ranging from 18 to 33 months) from a previous median of 1.5 years with a range of 9 to 24 months. At the time of last follow up, the median age of treated patients was 41.6 months (ranging from 30.2 to 53.3 months).

Biochemical data continue to be consistent with previously reported results and demonstrated sustained engraftment, supraphysiological levels of N-sulphoglucosamine sulphohydrolase (SGSH) enzyme and significant reduction of abnormal heparan sulfate levels in all compartments including the central nervous system. Treatment with OTL-201 was generally well-tolerated in the study population. No serious adverse events (SAEs) have been reported as of the recent data cut-off and there has been no evidence of insertional oncogenesis or clonal dominance in samples analyzed to date.

Updated neurocognitive results show:

- With extended follow-up, four out of five patients continued to gain cognitive skills in line with development in healthy children. Two patients were able to progress to a more advanced cognitive test (Kaufman scale, KABC-II), which has not been observed in natural history patients due to progression of disease and cognitive impairment.
- Evidence of developmental gains including acquisition of speech, continence and complex play requiring concentration which are not seen in untreated MPS-IIIA natural history patients was also observed in treated patients.

MPS-IIIA represents a significant medical need given there are no approved therapies and treatment with allogeneic HSCT has not been shown to be effective for this patient population. Patients enrolled in the ongoing proof-of-concept trial will be followed for a minimum of three years during which time the study investigators will continue to report additional biochemical and clinical outcomes.

“The recent follow-up from treated patients provide even more encouraging results for children living with MPS-IIIA and their families, who currently have no effective treatment options,” said Brian Bigger, professor of gene and cell therapy at the University of Manchester (UoM). “With follow-up now extending to more than two years in most patients, we continue to see sustained metabolic correction in the periphery and CNS. The maturing neurocognitive findings continue to suggest modification of the neurological phenotype. Two children have now progressed to the Kaufman scale—a first at Manchester Foundation Trust for MPS-IIIA patients with the severe phenotype.”

OTL-204 (GRN-FTD) Preclinical Data Summary

Today’s oral session is the first presentation supporting preclinical efficacy of OTL-204 in the progranulin form of frontotemporal dementia (GRN-FTD). Orchard, in collaboration with Dr. Alessandra Biffi at the University of Padua (UNIPD), developed therapeutic lentiviral vectors expressing the human GRN gene that were tested and validated using *in vitro* studies.

Data from *in vivo* studies indicate effective GRN protein delivery to the CNS of knockout mice transplanted with gene-modified HSCs. A therapeutic effect in transplanted knockout mice is evidenced by normalization of glucosylsphingosine, a specific lipid biomarker in the plasma, a strong reduction of lipofuscinosis and microgliosis, as well as markers of neuroinflammation in the thalamus, hippocampus and prefrontal cortex. Cohorts of knockout mice are being further evaluated both at behavioral and pathological level to accumulate additional evidence supporting the therapeutic approach.

“These findings highlight the potential of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers in a severe and common form of dementia,” said Fulvio Mavilio, Ph.D., chief scientific officer of Orchard Therapeutics. “Given the unique ability of HSCs to self-renew, differentiate into multiple cell types and cross the blood-brain-barrier, this approach is uniquely suited to potentially provide a one-time, curative treatment for patients and their families. We are encouraged by these positive findings and look forward to further evaluating the behavioral and pathological effects of OTL-204 in this preclinical model.”

Conference Call and Webcast
A live webcast will be available under "News & Events" in the Investors & Media section of the company's website at www.orchard-tx.com on Tuesday, May 23, 2023, at 8:00 a.m. EDT. Analysts who would like to ask questions at the end of the presentation should register here. A replay of the webcast will be archived on the Orchard website following the presentation.

About OTL-203 and MPS-I
Mucopolysaccharidosis type I (MPS-I) is a rare, inherited neurometabolic disease caused by a deficiency of the alpha-L-iduronidase (IDUA) lysosomal enzyme, which is required to break down sugar molecules called glycosaminoglycans (also known as GAGs). The accumulation of GAGs across multiple organ systems results in multiple symptomatic manifestations of the disease including severe neurocognitive impairment, skeletal deformities, cardiovascular and pulmonary complications, impaired motor function, loss of hearing and corneal clouding. MPS-I occurs at an overall estimated frequency of one in every 100,000 live births. There are three subtypes of MPS-I; approximately 60 percent of children born with MPS-I have the most severe subtype, called Hurler syndrome (MPS-IH), and rarely live past the age of 10 when untreated.

Treatment options for MPS-IH include allogeneic hematopoietic stem cell transplant and chronic enzyme replacement therapy, both of which have limitations. Though early intervention with enzyme replacement therapy has been shown to delay or prevent some clinical features of the condition, it has only limited efficacy on neurological symptoms. OTL-203 is an investigational ex vivo autologous hematopoietic stem cell gene therapy being studied for the treatment of MPS-IH. Orchard was granted an exclusive worldwide license to intellectual property rights to research, develop, manufacture and commercialize the gene therapy program for the treatment of MPS-IH developed by the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy.

About OTL-201 and MPS-IIIA
Mucopolysaccharidosis type IIIA (MPS-IIIA), also known as Sanfilippo syndrome type A, is a rare and life-threatening metabolic disease. People with MPS-IIIA are born with a mutation in the *N-sulphoglucosamine sulphohydrolase (SGSH)* gene which, when healthy, helps the body break down the sugar molecule heparan sulfate. The buildup of heparan sulfate in the brain and other tissues leads to intellectual disability and loss of motor function. MPS-IIIA occurs in approximately one in every 100,000 live births. Life expectancy of children born with MPS-IIIA is estimated to be between 10-25 years.

OTL-201 is an investigational hematopoietic stem cell gene therapy being developed for the treatment of MPS-IIIA. It uses a lentiviral vector to insert a functional copy of the human *SGSH* gene into a patient's hematopoietic stem cells. The OTL-201 program and this investigator-led clinical trial follow over a decade of development and pre-clinical work by Brian Bigger, Ph.D., professor of cell and gene therapy at University of Manchester (UoM). OTL-201 has received rare pediatric disease designation from the U.S. Food and Drug Administration (FDA) and is currently being evaluated in an ongoing proof-of-concept clinical trial sponsored by UoM, conducted at Royal Manchester Children's Hospital, and funded by Orchard Therapeutics.

About OTL-204 and FTD
Frontotemporal dementia (FTD) refers to a group of disorders caused by progressive damage to neurons in the frontal and temporal lobes of the brain. Symptoms include changes in behavior or personality, emotional problems, trouble communicating, difficulty with work, or difficulty walking. FTD tends to occur at a younger age than other forms of dementia with roughly 60 percent of people with FTD between 45 and 64 years of age, according to the NIH National Institute of Aging.

There is currently no cure or treatment for FTD with mortality occurring 3 to 4 years from diagnosis. Epidemiological studies suggest the FTD prevalent population in the U.S. and Europe is more than 50,000 patients with approximately 5% caused by mutations in the GRN gene, resulting in up to 2,500 GRN-FTD prevalent patients in the U.S. and Europe, with approximately 800 new patients diagnosed each year.

Orchard's preclinical program OTL-204 for GRN-FTD seeks to introduce a working copy of the GRN gene into a person's own HSCs, which can differentiate into microglia and secrete progranulin in the central nervous system, potentially correcting the underlying cause of the disease. Development work in GRN-FTD is being undertaken as part of a collaboration with Prof. Alessandra Biffi, chair of the Pediatric Hematology, Oncology and Stem Cell Transplant Division at the University of Padua (UNIPD).

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
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 forward-looking statements, which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Forward-looking statements include express or implied statements relating to, among other things, Orchard's business and product development strategy and goals, including the therapeutic potential of the programs mentioned in this press release, Orchard's expectations with respect to regulatory submissions for its product candidates, and 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, and the likelihood that data from clinical trials will be positive and support further clinical development and regulatory approval of Orchard's product candidates. 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 will not continue or be repeated in Orchard's ongoing or planned clinical trials, will be insufficient to support regulatory submissions or support or maintain marketing approval in the US or European Union, or that long-term adverse safety findings may be discovered; and the risk that any one or more of Orchard's product candidates will not be approved, successfully developed or commercialized. 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.

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[i] *Schmidt et al. Orphanet Journal of Rare Diseases (2016) 11:93 and Cattoni et al. Mol Genet Metab Rep 2021*

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