



Orchard Therapeutics Announces New England Journal of Medicine Publication of HSC Gene Therapy Data for ADA-SCID

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100% overall survival and ≥95% event-free survival observed at two and three years following one-time treatment with lentiviral HSC gene therapy

50 total participants represent largest published dataset of gene therapy-treated patients with a monogenic condition to date

BOSTON and LONDON, May 11, 2021 (GLOBE NEWSWIRE) -- Orchard Therapeutics (Nasdaq: ORTX), a global gene therapy leader, today announced data published in the *New England Journal of Medicine (NEJM)* evaluating the safety and efficacy of investigational gene therapy products, including OTL-101, for the treatment of adenosine deaminase severe combined immunodeficiency (ADA-SCID). Fifty (50) ADA-SCID patients were treated with investigational gene therapy composed of autologous CD34⁺ hematopoietic stem cells (HSCs) transduced *ex vivo* with a self-inactivating lentiviral vector (LVV) encoding the human *ADA* gene. Results showed 100% overall survival and ≥95% event-free survival (defined as survival in the absence of enzyme replacement therapy reinstatement or rescue allogeneic hematopoietic stem cell transplant (HSCT)) at two and three years.

The data were taken from three Phase 1/2 clinical studies (n=40), two conducted in the U.S. and one in the UK, as well as from a compassionate use program (n=10) in the UK. Results also showed sustained *ADA* gene expression, metabolic correction, and functional immune reconstitution in 48 out of the 50 patients. Discontinuation of immunoglobulin replacement therapy (IgRT) was seen in 26 out of 29 U.S. study patients (90%) who demonstrated sustained engraftment by two years and 19 out of 19 UK study patients (100%) who had sustained engraftment by three years. Additionally, no deaths, monoclonal expansion events, leukoproliferative complications, or emergence of replication-competent lentivirus were observed.

"Results from a one-time treatment with experimental lentiviral HSC gene therapy for ADA-SCID are compelling, most notably the overall and event-free survival rates (100% and ≥95%, respectively) observed at two and three years post-treatment," said Donald Kohn, M.D., distinguished professor of Microbiology, Immunology & Molecular Genetics and Pediatrics at the University of California, Los Angeles (UCLA), member of the UCLA Broad Stem Cell Research Center, director of the UCLA Human Gene and Cell Therapy Program, and co-lead author of the *NEJM* paper. "We saw no reports of graft versus host disease, and the ability to discontinue immunoglobulin replacement therapy over time in most patients is also notable for the gene therapy, contributing to its overall benefit-risk profile as a potential treatment for ADA-SCID."

ADA-SCID is a rare and life-threatening primary immunodeficiency caused by a genetic mutation that affects white blood cell production. Patients with ADA-SCID suffer from frequent, severe infections as well as non-immune symptoms including those affecting the gastrointestinal, skeletal and nervous systems. Without treatment, children born with ADA-SCID typically pass away by 2 years of age.

"With sustained engraftment of up to three years, these data show the potential of HSC gene therapy to correct the underlying genetic cause of ADA-SCID, delivering positive outcomes in a single treatment," said Bobby Gaspar, M.D., Ph.D., chief executive officer of Orchard Therapeutics. "We are encouraged by the results we've seen across this large dataset of 50 treated patients, and believe they reinforce the promise of the HSC gene therapy approach for treating and potentially curing certain life-threatening genetic diseases."

Results of Phase 1/2 Clinical Studies for *ex vivo* LVV HSC Gene Therapy

Fifty patients with ADA-SCID were treated with an investigational gene therapy composed of autologous CD34⁺ HSCs transduced *ex vivo* with a self-inactivating LVV encoding the human *ADA* gene. Thirty (30) subjects enrolled in the U.S. studies received OTL-101 as part of the registrational trials, which were conducted at the University of California, Los Angeles (UCLA), and the National Institutes of Health (NIH). Study patients in the UK received a very similar investigational HSC gene therapy product based on the same *ADA* LVV. An analysis was conducted to assess the safety and efficacy of the gene therapy for the treatment of ADA-SCID, which integrated two prospective, nonrandomized, Phase 1/2 clinical studies in the U.S. (using fresh and cryopreserved formulations) at two years' follow-up, alongside a prospective, nonrandomized Phase 1/2 clinical study conducted in the UK (fresh formulation) and compassionate use patients treated with the same UK protocol with three years' follow-up, used as supportive evidence.

Efficacy Data

Results published in *NEJM* from all 50 patients treated across the studies showed:

- Overall survival was 100% through the end of follow-up (two years for U.S. study patients and three years for UK study patients). At one year, event-free survival was 97% in U.S. study patients and 100% in UK study patients. Event-free survival remained at 97% in U.S. study patients at two years and was 95% in UK study patients at two and three years.
- Forty-eight of the 50 study patients successfully engrafted. Sustained vector copy number (VCN) was observed in granulocytes through the end of follow-up, and VCN continued to increase in peripheral blood mononuclear cells (PBMCs) up to two years in all study patients and was sustained up to three years in UK study patients.
- Median *ADA* enzyme activity in erythrocytes increased sharply in the first three months after treatment and remained within or above levels observed in healthy children at the last follow-up.

- Median total deoxyadenosine nucleotide levels and median deoxyadenosine triphosphate levels in U.S. and UK study patients, respectively, remained well below the maximum threshold indicating adequate detoxification through to last follow-up.
- At last follow-up, lymphocyte counts in most study patients achieved or came close to achieving the expected normal ranges for age. As expected, median T-cell and T-cell subset counts decreased following conditioning and enzyme replacement therapy withdrawal but recovered starting at month three post-treatment, with increases sustained through end of follow-up.
- Twenty-six (26) out of 29 U.S. study patients (90%) and 19 out of 19 (100%) UK study patients who showed sustained engraftment discontinued IgRT by year two or three, respectively. Median immunoglobulin G (IgG) levels remained high following cessation of IgRT.

Results were comparable in U.S. study patients receiving the fresh formulation with those receiving the cryopreserved formulation as shown by median VCN in granulocytes and PBMCs, median CD3⁺ T-cell levels, and median ADA activity.

Safety Data

Across all patients, no deaths, events of monoclonal expansion, leukoproliferative complications, or emergence of replication-competent lentivirus were noted. Adverse events were reported in all patients, most of which were mild or moderate and considered related to conditioning. No autoimmune or graft versus host (GvHD) events were noted.

Two U.S. study patients and two UK study patients had serious adverse events of immune reconstitution inflammatory syndrome (IRIS), beginning approximately 3 and 14 months and 3 and 22 months post-infusion, respectively. These events were considered unrelated to gene therapy, resolved with supportive therapy and were linked to transitory immune dysregulation during immune reconstitution.

About ADA-SCID and OTL-101

ADA-SCID is a rare, life-threatening, inherited disease of the immune system caused by mutations in the *ADA* gene resulting in a lack of, or minimal, immune system development.¹⁻⁴ The first symptoms of ADA-SCID typically manifest during infancy with recurrent severe bacterial, viral and fungal infections and overall failure to thrive, and without treatment the condition can be fatal within the first two years of life. The incidence of ADA-SCID is currently estimated to be one in 500,000 live births in the United States and between one in 200,000 and one in 1 million in Europe.³ OTL-101 is an investigational autologous *ex vivo* lentiviral hematopoietic stem cell-based gene therapy for the treatment of patients diagnosed with ADA-SCID. The registrational trials for OTL-101 recently concluded and were conducted at the University of California, Los Angeles (UCLA) and the National Institutes of Health (NIH). Orchard has worldwide rights to the OTL-101 program through license agreements with University of California, Los Angeles (UCLA), and UCL Business, Ltd. OTL-101 has received orphan drug designation from the FDA and the EMA for the treatment of ADA-SCID and Breakthrough Therapy Designation from the FDA. OTL-101 has also received a Rare Pediatric Disease Designation from the FDA.

The research was funded by Orchard Therapeutics with support from the National Institute of Allergy and Infectious Diseases, the National Heart, Lung and Blood Institute, and the National Human Genome Research Institute (all part of the U.S. National Institutes of Health); the California Institute for Regenerative Medicine; the U.K. National Institute for Health Research's Biomedical Research Centre at Great Ormond Street Hospital for Children National Health Service Foundation Trust and University College London.

About Orchard Therapeutics

Orchard Therapeutics is a global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. In 2018, Orchard 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. Orchard now has one of the deepest and most advanced gene therapy product candidate pipelines in the industry spanning multiple therapeutic areas where the disease burden on children, families and caregivers is immense 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, and the therapeutic potential of Orchard's product candidates, including the product candidate or candidates referred to in this release. 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 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, will be insufficient to support regulatory submissions or marketing approval in the US or EU, as applicable, 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 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 in the EU; 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 Annual Report on Form 10-K for the year ended December 31, 2020, 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.

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¹Orphanet. SCID due to ADA deficiency. ²Whitmore KV, Gaspar HB. *Front Immunol.* 2016;7:314. ³Kwan A, et al. *JAMA.* 2014;312:729-738. ⁴Sauer AV, et al. *Front Immunol.* 2012;3:265.