Ultragenyx Announces Positive Multi-Year Durability Data from Ongoing Phase 1/2 Gene Therapy Studies and Data on HeLa 3.0 Manufacturing Platform at American Society of Gene & Cell Therapy 2021 Annual Meeting

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Durable and Clinically Meaningful Responses Maintained at More than 2.5 and 3 Years Post-Treatment in Phase 1/2 Studies of DTX401 for GSDIa and DTX301 for OTC

Next-Generation HeLa Producer Cell Line Manufacturing Platform Results in Significant Product Yield Increases

NOVATO, Calif., May 14, 2021 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), a biopharmaceutical company focused on the development and commercialization of novel therapies for rare and ultra-rare diseases, today announced positive longer-term data from the Glycogen Storage Disease Type Ia (GSDIa) and Ornithine Transcarbamylase (OTC) Deficiency Phase 1/2 studies demonstrating ongoing durability of response, as well as data highlighting further advancements to the company's proprietary HeLa producer cell line (PCL) manufacturing platform. Data were presented this week at the American Society of Gene & Cell Therapy (ASGCT) 24th Annual Meeting.

"In the GSDIa and OTC programs, the durable responses coupled with the successful implementation of prophylactic steroids are encouraging as we move into our pivotal Phase 3 studies for these programs this year," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "We have also made significant progress with the latest 3.0 generation of our proprietary HeLa PCL manufacturing platform that will allow even greater product yield at the 2000 liter scale while maintaining or even improving product quality. This enables us to study larger disease indications and expand into central nervous system and muscle disorders that may require higher doses, all while continuing to drive down AAV production costs."

DTX401 (GSDIa) Program

Longer-term Phase 1/2 data demonstrate durability of response, with sustained responses lasting more than 2.5 years since treatment

All nine patients continue to demonstrate improved glucose control while tapering or discontinuing oral glucose replacement with cornstarch and improvements in energy metabolism pathways over the long term, with patients in the first cohort sustaining responses more than 2.5 years since treatment. Patients continue to taper the amount and frequency of cornstarch dosing reaching an overall mean reduction of cornstarch intake of 79% (p-value<0.0001) by their latest visit (ranging from 60 weeks to 131 weeks). In Cohort 3 continuous glucose monitoring was implemented, and data indicate that these patients achieved significant cornstarch reductions while increasing the time spent in euglycemia, defined by blood glucose levels in the normal range of 60 to 120 mg/dL.

All three patients in the prophylactic steroid cohort are doing well and have demonstrated early reduction in daily cornstarch intake

All patients in the prophylactic cohort in the Phase 1/2 study have demonstrated early, clinically meaningful cornstarch reductions ranging from 64% to 83%. One of the patients has recently completed the prophylactic course of steroids, and the other two continue to taper steroids.

Across the Phase 1/2 study, there have been no infusion-related adverse events and no treatment-related serious adverse events (SAEs) reported.

Phase 3 study of DTX401 in GSDIa expected to initiate early in the second half of 2021

The Phase 3 study has a 48-week primary efficacy analysis period and will enroll approximately 50 patients, randomized 1:1 to DTX401 (1.0 x 10^13 GC/kg dose) or placebo. The primary endpoint is expected to be the reduction in oral glucose replacement with cornstarch while maintaining or improving glucose control assessed by continuous glucose monitoring. The study design has been submitted and endpoints are being finalized with regulators.

DTX301 (OTC) Program

Longer-term Phase 1/2 data show durable metabolic control and sustained responses lasting more than three years since treatment

The six patients who previously demonstrated a response remain clinically and metabolically stable, including all three treated at the highest dose (1.7 x 10^13 GC/kg dose), which is the dose that will be used in the Phase 3 study. Some patients have now

demonstrated a durable response three years after treatment, and more than two years after discontinuing ammonia-scavenger medications and liberalizing protein-restricted diets. All responders remain in excellent clinical condition with no significant adverse events, hospitalizations, or other events related to OTC deficiency.

Prophylactic steroid cohort: Both patients dosed; first patient has demonstrated a response, second patient responder status will be evaluated after patient finishes steroid regimen
Both patients in the prophylactic steroid cohort are doing well clinically with good metabolic control and without any safety issues. The first patient has maintained normal ammonia levels and has reduced their ammonia-scavenger drug by 45% so far, following completion of the prophylactic course of steroids. This patient is continuing to taper medications. The second patient continues to taper their course of steroids, and changes in ammonia-scavenging drugs or diet will only be attempted after the prophylactic steroid taper is complete. This patient has maintained normal ammonia levels since treatment.

Across all cohorts of the Phase 1/2 study, there have been no infusion-related adverse events and no treatment-related serious adverse events reported. All treatment-related adverse events have been Grade 1 or 2.

Phase 3 study to initiate in second half 2021
The Phase 3 study will include a 64-week primary efficacy analysis period and enroll approximately 50 patients 12 years of age and older, randomized 1:1 to DTX301 (1.7 x 10^13 GC/kg dose) or placebo. The co-primary endpoints are the percentage of patients who achieve a response as measured by discontinuation or reduction in baseline disease management and the 24-hour plasma ammonia levels.

HeLa 3.0 Producer Cell Line (PCL) advancements significantly increase productivity of the platform
Data on the HeLa 3.0 platform demonstrated that genetic engineering of the HeLa cell significantly improved AAV production. This increased productivity was achieved while maintaining or improving product quality. Permanent knockout of target genes identified by RNA sequencing (HeLa 3.0) was shown to increase titer in established PCLs (HeLa 2.0), and the single knockout HeLa 3.0 PCLs displayed similar phenotype to parental PCLs (HeLa 2.0) during production. These cell line engineering improvements result in a 2- to 5-fold yield improvement over the HeLa 2.0 platform, and a 50-fold yield improvement over HeLa 1.0. Additional improvements in yield are expected with future combinatorial knockdowns, with early studies suggesting a further 5-to 10-fold improvement.

These improvements in the HeLa platform allow for increased productivity and reproducibility with higher full-to-empty AAV ratios while continuing to drive down AAV production costs, all important attributes in the manufacturing of gene therapies for diseases where high product yield is required.

About GSDIa and DTX401

GSDIa is the most severe genetically inherited glycogen storage disease. It is caused by a defective gene coding for the enzyme G6Pase-α, resulting in the inability to regulate blood sugar (glucose). Hypoglycemia in patients with GSDIa can be life-threatening, while the accumulation of the complex sugar glycogen in certain organs and tissues can impair the ability of these tissues to function normally. If chronically untreated, patients can develop severe lactic acidosis, progress to renal failure, and potentially die in infancy or childhood. There are no approved pharmacologic therapies. An estimated 6,000 patients worldwide are affected by GSDIa.

DTX401 is an investigational AAV8 gene therapy designed to deliver stable expression and activity of G6Pase-α under control of the native promoter. DTX401 is administered as a single intravenous infusion and has been shown in preclinical studies to improve G6Pase-α activity and reduce hepatic glycogen levels, a well-described biomarker of disease progression. DTX401 has been granted Orphan Drug Designation in both the United States and Europe, and Regenerative Medicine Advanced Therapy (RMAT) designation and Fast Track designation in the United States.

About OTC Deficiency and DTX301

OTC deficiency, the most common urea cycle disorder, is caused by a genetic defect in a liver enzyme responsible for detoxification of ammonia. Individuals with OTC deficiency can build up excessive levels of ammonia in their blood, potentially resulting in acute and chronic neurological deficits and other toxicities. It is estimated that more than 10,000 people are affected by OTC deficiency worldwide, of whom approximately 80 percent are classified as late-onset and represent a clinical spectrum of disease severity. In the late-onset form of the disease, elevated ammonia can lead to significant medical issues for patients. Neonatal onset disease occurs only in males, presents as severe disease, and can be fatal at an early age. Approved therapies, which must be taken multiple times a day for the patient's entire life, do not eliminate the risk of future metabolic crises. Currently, the only curative approach is liver transplantation.

DTX301 is an investigational AAV type 8 gene therapy designed to deliver stable expression and activity of OTC following a single intravenous infusion. It has been shown in preclinical studies to normalize levels of urinary orotic acid, a marker of ammonia

metabolism. DTX301 was granted Orphan Drug Designation in both the United States and Europe.

About Ultragenyx Pharmaceutical Inc.
Ultragenyx is a biopharmaceutical company committed to bringing novel therapies to patients for the treatment of serious rare and ultra-rare genetic diseases. The company has built a diverse portfolio of approved medicines and treatment candidates aimed at addressing diseases with high unmet medical need and clear biology, for which there are typically no approved therapies treating the underlying disease.

The company is led by a management team experienced in the development and commercialization of rare disease therapeutics. Ultragenyx's strategy is predicated upon time- and cost-efficient drug development, with the goal of delivering safe and effective therapies to patients with the utmost urgency.

For more information on Ultragenyx, please visit the company's website at: www.ultragenyx.com.

Forward-Looking Statements

Except for the historical information contained herein, the matters set forth in this press release, including statements related to Ultragenyx's expectations and projections regarding its future operating results and financial performance, anticipated cost or expense reductions, the timing, progress and plans for its clinical programs and clinical studies, future regulatory interactions, and the components and timing of regulatory submissions are forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements involve substantial risks and uncertainties that could cause our clinical development programs, collaboration with third parties, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the effects from the COVID-19 pandemic on the company's clinical activities, business and operating results, risks related to reliance on third party partners to conduct certain activities on the company's behalf, uncertainty and potential delays related to clinical drug development, smaller than anticipated market opportunities for the company's products and product candidates, manufacturing risks, competition from other therapies or products, and other matters that could affect sufficiency of existing cash, cash equivalents and short-term investments to fund operations, the company's future operating results and financial performance, the timing of clinical trial activities and reporting results from same, and the availability or commercial potential of Ultragenyx's products and drug candidates. Ultragenyx undertakes no obligation to update or revise any forward-looking statements. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of Ultragenyx in general, see Ultragenyx's Quarterly Report on Form 10Q filed with the Securities and Exchange Commission on May 5, 2021, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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