# Ultragenyx Announces Positive Longer-term Durability Data from Two Phase 1/2 Gene Therapy Studies at American Society of Gene & Cell Therapy (ASGCT) 2022 Annual Meeting

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*Durable and clinically meaningful responses sustained for more than three years post-treatment in study of DTX401 for GSDIa and four or more years in study of DTX301 for OTC*

NOVATO, Calif., May 19, 2022 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), a biopharmaceutical company focused on the development and commercialization of novel products for serious rare and ultra-rare genetic diseases, today announced positive longer-term efficacy and safety data from Phase 1/2 studies of DTX401 for the potential treatment of Glycogen Storage Disease Type Ia (GSDIa) and DTX301 for the potential treatment of Ornithine Transcarbamylase (OTC) deficiency. Results demonstrate ongoing durability of response and safety for both gene therapy programs as of the data cutoff date. Data were presented this week at the American Society of Gene & Cell Therapy (ASGCT) 25$^{th}$ Annual Meeting.

"We are encouraged by the longer-term durable responses and metabolic stability we continue to observe in our lead gene therapy programs and the progress we're making toward bringing these investigational gene therapies to patients with GSDIa and OTC," said Eric Crombez, M.D., Chief Medical Officer, Ultragenyx Gene Therapy and Inborn Errors of Metabolism. "The potential to establish normal metabolism with gene therapy could allow these patients to live without restrictive or burdensome diets and medications and lead to increased quality of life."

**DTX401 (GSDIa) Phase 1/2 Update**
*Longer-term Phase 1/2 data demonstrate durability of response, with sustained responses lasting more than 3.5 years since treatment*

All 12 patients in the study continue to demonstrate improved glucose control, experiencing reductions in oral glucose replacement with cornstarch. Overall, patients reached a mean total daily reduction of cornstarch intake of 70% (p-value<0.0001) from baseline to the last available timepoint. Three patients in the first cohort have sustained responses for up to 3.5 years since treatment.

Continuous glucose monitoring was introduced in the third cohort, and data indicate that these patients achieved significant reductions in average cornstarch intake while increasing the time spent in euglycemia, defined by blood glucose levels in the normal range of 60 mg/dL to 120 mg/dL. Specifically, average cornstarch intake was reduced by 65% at Weeks 49 to 52 compared with Weeks 1 to 4, while euglycemia increased by 14% in the same period.

All three patients in the fourth cohort have completed a tapering prophylactic steroid regimen and have demonstrated reductions in daily cornstarch intake, while the average percentage of time in euglycemia for these patients remained stable.

When patients were interviewed at 52 weeks, they reported more energy and stamina, better mental clarity, improved glycemic control independent from cornstarch, improved sleep quality and improvements in health-related quality of life related to cornstarch intake reduction. Patient Global Impression of Change (PGIC) scores at the Week 52 visit indicated that 67% of patients (n=9) felt their GSDIa was moderately or much improved since the start of the study.
Across the Phase 1/2 study, there have been no infusion-related adverse events and no treatment-related serious adverse events (SAEs) reported.

**DTX301 (OTC) Phase 1/2 Update**
*Longer-term Phase 1/2 data show durable metabolic control and sustained responses lasting more than four years since treatment*

Four out of the five patients treated at the highest dose (1.7 x 10^13 GC/kg dose) – the dose specified for the Phase 3 study – have responded and remain clinically and metabolically stable. Overall, the seven responders of the 11 total patients treated across all cohorts remain clinically and metabolically stable. Six patients enrolled in the first three cohorts demonstrated durable response with 2 to 4.5 years of follow-up after treatment. One patient enrolled in the last cohort also achieved complete response prior to the 1-year follow-up. Four complete responders have discontinued ammonia-scavenger medications and liberalized their diet within one year.

In the prophylactic steroid cohort, one of two patients demonstrated a complete response. The second patient was a responder at week 36, but viral infections and an inability to sustain increased protein intake in the presence of lowered medication led to catabolism. The patient was considered a nonresponder as of the 52-week visit. Once the patient is metabolically stable, we will reinitiate tapering of baseline disease management.

Across all cohorts of the Phase 1/2 study, no treatment-related serious adverse events, infusion-associated reactions or dose-limiting toxicities have been reported. All reported adverse events have been Grade 1 or 2 during the main study except for one patient with Grade 3 hyperammonemic crises assessed as unrelated to DTX301. All patients have enrolled in the six-year extension study. No patient who received corticosteroids experienced an AE of increased ammonia, hyperammonemia, or hyperammonemic crisis (HAC) that was associated with corticosteroid administration.

**About GSDIa and DTX401**
GSDIa is a serious 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.

In addition to the Phase 1/2 study, DTX401 is being evaluated in the Phase 3 *GlucoGene* study. The 48-week study will enroll approximately 50 patients aged eight and older randomized 1:1 to DTX401 (1.0 x 10^13 GC/kg dose) or placebo. The primary endpoint is the reduction in oral glucose replacement with cornstarch while maintaining glucose control.

**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 AAV8 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.

In addition to the Phase 1/2 study, Ultragenyx plans to initiate the Phase 3 *Enh$_3$ance* study of DTX301 in patients with OTC in mid-2022. The 64-week study will include approximately 50 patients, randomized 1:1 to DTX301 or placebo. The primary endpoints are complete response as measured by discontinuation of baseline disease management and ammonia control as measured by 24-hour ammonia levels, supported by patient-reported outcomes, rate of hyperammonemic crises, and assessment of executive function.

**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 and Use of Digital Media**
*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 and commercial activities and 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, the company's ability to achieve its projected development goals in its expected timeframes, risks and uncertainties related to the regulatory approval process, 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 10-Q filed with the Securities and Exchange Commission (SEC) on May 5, 2022, and its subsequent periodic reports filed with the SEC. In addition to its SEC filings, press releases and public conference calls, Ultragenyx uses its investor relations website and social media outlets to publish important information about the company, including information that may be deemed material to investors, and to comply with its disclosure obligations under Regulation FD. Financial and other information about Ultragenyx is routinely posted and is accessible on Ultragenyx's investor relations website (https://ir.ultragenyx.com/) and LinkedIn website (https://www.linkedin.com/company/ultragenyx-pharmaceutical-inc-/).*

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