# Ultragenyx Announces Positive Data from Confirmatory Cohort of Phase 1/2 Study of DTX401 Gene Therapy for Glycogen Storage Disease Type Ia (GSDIa)

May 15, 2020

*All Patients in Cohort 3 Demonstrate Increased Time to Hypoglycemia and a Substantial Reduction in Cornstarch Use*

*Introduction of Continuous Glucose Monitoring Reveals Early Transgene Expression and Enables More Rapid Reduction in Cornstarch*

*Ultragenyx to Host ASGCT Recap Investor Conference Call today at 8:30 a.m. Eastern Time*

NOVATO, Calif., May 15, 2020 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), a biopharmaceutical company focused on the development and commercialization of novel products for rare and ultra-rare diseases, today announced positive initial data from the confirmatory third cohort and longer-term data from the first two cohorts of the ongoing Phase 1/2 study of DTX401, an adeno-associated virus (AAV) based gene therapy for the treatment of glycogen storage disease type Ia (GSDIa). All three patients in Cohort 3 responded to therapy and demonstrated more rapid reductions in cornstarch requirements compared to the first two cohorts. Across all cohorts, 100 percent of patients (n=9) demonstrated meaningful and sustained cornstarch reductions over time and significant increases in time to hypoglycemia. Data from the Phase 1/2 study are being presented today at the American Society of Gene & Cell Therapy (ASGCT) virtual meeting.

“In the confirmatory third cohort, continuous glucose monitoring showed early transgene expression and enabled faster and more accurate reductions in cornstarch compared with prior cohorts,” said Eric Crombez, M.D., Chief Medical Officer of the Ultragenyx Gene Therapy development unit. “The use of continuous glucose monitoring offers the ability to better understand the improvement in glucose metabolism after treatment with DTX401 over the course of the entire day and on an ongoing basis.”

"We are extremely excited by the results being obtained in this first in human gene therapy trial for glycogen storage disease type Ia,” said David Weinstein, M.D., M.M.Sc., Professor and Director, Glycogen Storage Disease Program at Connecticut Children’s Medical Center and UConn Health. “The third cohort of patients is experiencing more rapid improvement with fasting and tolerating quicker reduction in their cornstarch therapy when compared with the prior cohorts. Most importantly, the benefits seen for patients are being maintained, and the majority of treated patients are now off of cornstarch therapy during the day after one year of treatment. In 26 years of caring for people with GSD, I have never seen this before, and the community is excited for the Phase 3 trial to commence.”

**Confirmatory Cohort 3 Amendments**
Based on results and lessons learned from Cohorts 1 and 2, three modifications were made to the protocol for the confirmatory Cohort 3. First, the cornstarch dose at the start of each controlled fasting challenge was reduced from 35 grams to 5 grams to reduce an acute rise in glucose followed by an insulin surge, resulting in early termination of the fasting challenge. Second, continuous glucose monitoring (CGM) was implemented to allow more accurate cornstarch management. Third, the reactive use of steroids was optimized to begin steroids earlier, when alanine aminotransferase (ALT) levels increase from baseline, even if still within the normal range.

**Efficacy Data Summary**
***Early Transgene Expression Demonstrated in Confirmatory Cohort 3***
In Cohort 3, CGM data showed early transgene expression within days of dosing with DTX401. This was demonstrated by prolonged periods of hyperglycemia, which is consistent with glucose being released from the liver and transgene expression.

***Rapid Cornstarch Reduction in Cohort 3 and Further Reduction in Earlier Cohorts***
In the confirmatory cohort, CGM enabled more rapid reduction of cornstarch intake following observations of hyperglycemia at home, which minimized the insulin response and provided more metabolic stability for patients. At Week 12, patients in Cohort 3 had reduced mean daily cornstarch intake by 57 percent, compared with 38 percent in the first cohort and 14 percent in the second cohort.

Patients in Cohort 1 and 2 continue to decrease cornstarch with a mean 73 percent reduction as of the data cutoff of April 23, 2020, demonstrating durable responses over time. Four of the six patients in the first two cohorts have now discontinued daytime cornstarch, and one patient has completely discontinued cornstarch.

***Optimized Reactive Steroids More Effectively Mitigated Elevations in Liver Transaminases***
Patients in Cohort 3 received an optimized reactive steroid regimen as soon as alanine aminotransferase (ALT) levels began to rise above baseline, at approximately Week 4 for all three patients in the cohort. This earlier steroid use was more effective at mitigating elevations in ALT, and could further enhance the level and consistency of expression that has been demonstrated.

***Early Improvements in Time to Hypoglycemia Observed for All Patients***
By decreasing the cornstarch at the beginning of the controlled fasting challenge, the mean baseline time to hypoglycemia decreased from 4.5 hours in Cohorts 1 and 2, to 2.3 hours in Cohort 3, with two patients in Cohort 3 under 2 hours. At week 12, all patients in Cohort 3 demonstrated meaningful increases in time to hypoglycemia. Patient 7 demonstrated a 167 percent increase (1.4 hours at baseline to 3.7 hours at Week 12). Patient 8 demonstrated a 23 percent increase (3.6 hours at baseline to 4.4 hours at Week 12). Patient 9 demonstrated a 60 percent increase (1.9 hours at baseline to 3.1 hours at Week 12).

Due to the COVID-19 pandemic, only Week 12 controlled fasting challenges have been conducted to date for Cohort 3, as patients were not able to complete the Week 24 in-hospital fasting challenges. It will be important to monitor these patients as they adapt to their lower cornstarch regimen to continue to assess their glucose metabolism.

***Safety Summary***
As of the cutoff date, there have been no infusion-related adverse events and no treatment-related serious adverse events reported. All adverse events have been Grade 1 or 2. Seven of the nine patients in the study had mild, asymptomatic ALT elevations, including all three patients in Cohort 3. These elevations were similar to what has been observed in other programs using AAV-based gene therapy, and were successfully treated with

reactive steroids. The optimized reactive steroid regimen used in Cohort 3 was more effective at rapidly mitigating elevations in ALT compared with earlier cohorts.

**DTX401 Phase 3 Study**
Ultragenyx is continuing to collect longer-term data from the Phase 1/2 study, which is expected to be available in the second half of 2020, barring further significant delays related to COVID-19. The company also intends to hold an end-of-Phase 2 meeting with the U.S. Food and Drug Administration (FDA) in the second half of 2020. The Phase 3 study could begin by the end of this year, depending on whether there are any COVID-19 related delays.

**Conference Call and Webcast Information**
Ultragenyx will host a conference call today, Friday May 15, 2020, at 8:30 a.m. ET/ 5:30 a.m. PT during which Emil D. Kakkis, M.D., Ph.D., the company's Chief Executive Officer and President, will discuss the new data from the DTX301 and DTX401 studies presented at ASGCT. The live and replayed webcast of the call and slides will be available through the company's website at http://ir.ultragenyx.com/events.cfm. To participate in the live call by phone, dial (855) 797-6910 (USA) or (262) 912-6260 (international) and enter the passcode 2366186. The replay of the call will be available for one year.

**DTX401 Phase 1/2 Study Design**
The open-label, multicenter Phase 1/2 study is evaluating the safety, tolerability and therapeutic response of DTX401 in adults with GSDIa. DTX401 is an AAV8 gene therapy expressing the glucose-6-phosphatase gene (G6Pase-α) under control of the native promoter. In the first cohort, three patients received a single 2.0 × 10^12 GC/kg dose of DTX401. In the second cohort, three patients each received a single 6.0 × 10^12 GC/kg dose of DTX401. In the confirmatory cohort, three patients received the same dose of DTX401 as in Cohort 2. Modifications were made to the protocol for the confirmatory cohort, including: reduction of cornstarch dose at the start of the controlled fasting challenge (decreased from 35 g to 5 g); use of CGM; implementation of an optimized reactive steroid regimen. Key efficacy assessments include time to hypoglycemia (defined as glucose <60 mg/dL or onset of clinical symptoms) during a controlled in-hospital fasting challenge, cornstarch reduction, impact on biomarkers such as lactic acid, and measurement of glycogen storage in liver by MRI.

**About GSDIa**
GSDIa is the most severe genetically inherited glycogen storage disease. It is caused by a defective gene 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.

**About DTX401**

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 Ultragenyx**
Ultragenyx is a biopharmaceutical company committed to bringing to patients novel products for the treatment of serious rare and ultra-rare genetic diseases. The company has built a diverse portfolio of approved therapies and product candidates aimed at addressing diseases with high unmet medical need and clear biology for treatment, 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 trial activities, business and operating results, smaller than anticipated market opportunities for the company's products and product candidates, manufacturing risks, the uncertainties inherent in the clinical drug development process, including the potential for substantial delays and the risk that earlier study results may not be predictive of future study results, the lack of predictability in the regulatory approval process, the timing of regulatory filings and approvals (including whether such approvals can be obtained), 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 on May 7, 2020, and its subsequent periodic reports filed with the Securities and Exchange Commission.*

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