Ultragenyx Announces Positive Longer-term Results from First Three Cohorts of Phase 1/2 Study of DTX301 Gene Therapy in Ornithine Transcarbamylase (OTC) Deficiency

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All three patients in Cohort 3 now confirmed responders

All three complete responders in the study remain clinically and metabolically stable after longer-term follow-up

Ultragenyx to host ASGCT recap investor conference call Friday, May 15 at 8:30 a.m. Eastern Time

NOVATO, Calif., May 13, 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 longer-term safety and efficacy data from the first three cohorts of the ongoing Phase 1/2 study of DTX301, an investigational adeno-associated virus (AAV) gene therapy for the treatment of ornithine transcarbamylase (OTC) deficiency. Six of nine patients in the study have responded to the gene therapy (three female, three male), including all three patients in Cohort 3 who are now confirmed responders. The three previously disclosed complete responders, who have discontinued all ammonia scavengers and liberalized their diet, remain clinically and metabolically stable after longer-term follow-up. Data from the Phase 1/2 study were presented today at the American Society of Gene & Cell Therapy (ASGCT) virtual 2020 Annual Meeting.

“We are seeing durable and clinically meaningful responses to DTX301. We are extremely encouraged that the patients who have stopped alternate pathway medications and liberalized dietary restrictions continue to do very well over these longer periods of time,” said Eric Crombez, M.D., Chief Medical Officer of the Ultragenyx Gene Therapy development unit. “The recent data also reinforces the higher response rate seen with the Cohort 3 dose of 1x10^13 GC/kg. All three patients in Cohort 3 have responded to DTX301 and the treating physician of one of these patients reported that this is the best she has been health wise. This dose has been selected for the Phase 3 study, which is currently expected to initiate in the first half of 2021.”

Cohort 3 Updated Data: All three patients at 1x10^{13} GC/kg dose now confirmed responders

Patient 9 (newly confirmed responder, male):
Patient 9 showed a 188 percent increase in rate of ureagenesis, from 25 percent of normal at baseline to 73 percent of normal at Week 24. He now has shown two significantly increased ureagenesis measures and is confirmed as a responder. His ammonia levels have remained in the normal range since treatment. He has not yet discontinued alternate pathway medications or liberalized his diet.

Patient 8 (previously disclosed responder, female):
As previously disclosed, Patient 8 has experienced a significant and sustained reduction in her elevated baseline ammonia levels. This patient has now increased protein intake and has discontinued one of her two ammonia scavenger medications. She continues to do well clinically and the plan is to begin to taper her second alternate pathway medication once she is able to return to clinic post COVID-19 restrictions.

Patient 7 (previously disclosed complete responder, female):
As previously disclosed, Patient 7 demonstrated a meaningful change in rate of ureagenesis and has maintained normal ammonia levels since treatment. She continues to be clinically and metabolically stable after liberalizing diet and discontinuing ammonia scavenger medications.

Cohorts 1 and 2 Long-term Data Show Sustained Efficacy
The two complete responders in Cohorts 1 and 2 (Patients 1 and 4) have shown ongoing durable responses for 2 years and 1.5 years, respectively. Their ureagenesis rates remain above 100% of normal. Both patients have discontinued alternate pathway medications and liberalized restricted protein diets for more than one year, and remain stable with ammonia levels maintained in the normal range. They remain in excellent clinical condition with no significant adverse events, hospitalizations, or other events related to OTC deficiency. The third responder from the earlier cohorts (Patient 6) continues to do well, and is currently tapering her medications and liberalizing her diet. Her increase in ureagenesis and normalization of ammonia have been maintained.

Safety Summary

As of the data cutoff date, there have been no infusion-related adverse events and no treatment-related serious adverse events reported in the study. All adverse events have been Grade 1 or 2. As previously reported, six patients experienced mild, clinically asymptomatic elevations in ALT levels, similar to what has been observed in other programs using AAV-based gene therapy. All six of these patients have responded to reactive tapering courses of steroids, and all patients remain clinically stable.

Prophylactic Steroid Cohort Planned
A fourth cohort of three patients at the Cohort 3 dose (1.0 × 10^13 GC/kg) is planned, using prophylactic steroids. Dosing in this cohort is currently on hold due to the COVID-19 pandemic, but data are still expected in the second half of 2020, barring further delays related to clinical site closures due to COVID-19.

Phase 3 Study Planning Underway
Ultragenyx is currently planning the Phase 3 study of DTX301 in parallel to conducting the prophylactic steroid cohort. The Company intends to hold an end of Phase 2 meeting with the U.S. Food and Drug Administration (FDA) in the second half of 2020, based on data from the first three cohorts of the Phase 1/2 study. The use of prophylactic steroids in the Phase 3 study is anticipated, and will be confirmed by the Phase 1/2 fourth cohort data once available. For the Phase 3 study, ammonia is expected to be a primary endpoint based on direct FDA feedback to date. The Phase 3 study is currently expected to begin enrollment in the first half of 2021, barring any significant delays due to COVID-19.

Conference Call and Webcast Information
Ultragenyx will host a conference call on 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.

About the OTC Phase 1/2 Study (DTX301)
The Phase 1/2 dose-escalation study evaluates the change in the rate of ureagenesis, ammonia levels, neurocognitive assessment, biomarkers, and safety of DTX301 in adult patients with OTC deficiency. Three patients have been dosed in each of three dose cohorts of 2.0 × 10^12 GC/kg (Cohort 1), 6.0 × 10^12 GC/kg (Cohort 2), and 1.0 × 10^13 GC/kg (Cohort 3). Patients in the first three cohorts received steroids to reactively manage ALT elevations. In the fourth cohort, three patients will receive a 1.0 × 10^13 GC/kg dose and will all receive a prophylactic tapering course of steroids.

About OTC Deficiency
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.

About DTX301
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
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.

Contact Ultragenyx Pharmaceutical Inc.
Investors & Media
Danielle Keatley
415-475-6876

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