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Ultragenyx Announces Positive Interim Topline Results From First Cohort of Phase 1/2 Clinical Study of DTX301 Gene Therapy in Ornithine Transcarbamylase (OTC) Deficiency

Early Evidence of Normalization of Ureagenesis in One Patient in Lowest-Dose Cohort and Acceptable Initial Safety Profile

NOVATO, Cali., Jan. 07, 2018 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), a biopharmaceutical company focused on the development of novel products for rare and ultra-rare diseases, today announced positive interim safety and efficacy data from the first dose cohort of the Phase 1/2 study of DTX301, an adeno-associated virus (AAV) gene therapy for the treatment of ornithine transcarbamylase (OTC) deficiency.

"We are encouraged by these initial data showing activity with our AAV8 vector in patients in the first, lowest-dose cohort. Patient 1 showed a normalization of ureagenesis that was maintained through 12 weeks, and we view this initial efficacy data as clinically meaningful and a promising indication of the potential of DTX301," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "Based on the data to date, we expect to be able to move to the higher-dose second cohort pending the data monitoring committee's review of the 12-week safety data for all three patients in this cohort, and data from this second cohort should be available in the second half of 2018."

DTX301 Interim Data Summary
The study is designed to enroll patients with late-onset disease who are clinically stable and on a stable dose of alternate pathway medication. All three patients in the first, lowest -dose cohort received a single DTX301 dose of 2.0 × 10^12 GC/kg. As of the December 22, 2017 data cutoff date, two of the three patients have been followed for at least 12 weeks, the pre-defined endpoint for efficacy evaluation, and the third patient has been followed for 6 weeks.

Safety Summary

As of December 22, 2017 there have been no infusion-related adverse events and no serious adverse events reported. All adverse events have been Grade 1 or 2 and have resolved. The only treatment-related adverse events were mild, clinically asymptomatic and manageable elevations in alanine aminotransferase (ALT) in two patients, peaking at 45 (Patient 1) and 118 IU/L (Patient 2). These ALT elevations were mild and similar to what has been observed in other programs using AAV gene therapy. Both patients completed a standard tapering course of corticosteroids to treat the ALT elevations, and as of the data cutoff date, their ALT levels were in the normal range (below 40 U/L). The third patient had ALTs that remained in the normal range through six weeks.

Efficacy Summary

The first patient's rate of ureagenesis was normalized and maintained over 12 weeks. Their rate of ureagenesis at baseline was 200 umol/kg/hr (67% of normal, defined as 300 umol/kg/hr). At 6 weeks, their rate of ureagenesis increased to 335 umol/kg/hr (67% increase from baseline, 112% of normal). At 12 weeks, their rate of ureagenesis was 261 umol/kg/hr (30% increase from baseline, 87% of normal). The second patient did not show a clinically meaningful change in rate of ureagenesis over the 12-week period. The third patient showed a modest increase in ureagenesis from baseline over the first six weeks of treatment. This patient has not yet reached the 12-week post-dosing point. This cohort dose is at the low end of the expected range and showed some signs of efficacy with an acceptable safety profile. The second cohort dose planned is 6.0 x 10^12 GC/kg and will be initiated after the third patient reaches 12 weeks and a DMC review is completed.

About the OTC Phase 1/2 Study (DTX301)

To evaluate therapeutic response of DTX301, the study measures the change in the rate of ureagenesis, the pathway for the metabolism of ammonia which is deficient in OTC patients. This is determined using a well-established stable 13C-acetate labeling approach. Ammonia levels, neurocognitive assessment, biomarkers, and safety will also be evaluated. There are three potential dose cohorts in the study. Patients in the first cohort received a dose of 2.0 × 10^12 GC/kg; patients in cohort 2 would receive a dose of 6.0 × 10^12 GC/kg; patients in cohort 3 would receive a dose of 1.0 × 10^13 GC/kg. The decision to proceed to the next, higher dose cohort will be made after the data monitoring committee (DMC)

evaluates the efficacy and safety data for all patients in the previous dosing cohort.

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 patients are affected by OTC deficiency worldwide, of which approximately 80% are classified as late-onset. In the late-onset form of the disease, elevated ammonia can lead to significant medical issues for patients who are in need of new disease-modifying therapies. The greatest percentage of patients, including males and females, experience late-onset disease, representing a clinical spectrum of disease severity. Neonatal onset disease occurs 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 and 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 to market novel products for the treatment of rare and ultra-rare diseases, with a focus on serious, debilitating genetic diseases. The Company has rapidly built and advanced a diverse portfolio of product candidates with the potential to address diseases for which the unmet medical need is high, the biology for treatment is clear, and for which there are no approved therapies.

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 relating to Ultragenyx's expectations regarding the timing of release of additional data for its product candidates, and plans for its clinical programs and its clinical studies, 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, 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 uncertainties inherent in the clinical drug development process, such as the regulatory approval process, the timing of regulatory filings, and other matters that could affect sufficiency of existing cash, cash equivalents and short-term investments to fund operations and the availability or commercial potential of our 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 November 3, 2017, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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