Ultragenyx Announces Positive Topline Results and DMC Review from First Cohort of Phase 1/2 Clinical Study of DTX301, an Investigational Gene Therapy in Ornithine Transcarbamylase (OTC) Deficiency

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Ureagenesis normalized in one patient and further increased by 24 weeks

Cohort 2 patient enrollment to begin in March 2018; data expected in second half of 2018

NOVATO, Calif., March 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 longer-term safety and efficacy data from the first dose cohort of the Phase 1/2 study of DTX301, an investigational adeno-associated virus (AAV) gene therapy for the treatment of ornithine transcarbamylase (OTC) deficiency.

“Longer term data from the first, lowest-dose cohort show that patient 1 maintained and substantially increased levels of ureagenesis through 24 weeks and we view these results as a promising indication of the potential and durability of DTX301. Based on these positive results at 24 weeks, this patient opted to discontinue all alternate pathway medication three weeks ago per the trial protocol and continues to do well,” said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. “The data monitoring committee has completed a favorable review of the current data for this dosing cohort. We were encouraged by the initial signs of efficacy with an acceptable safety profile in the first cohort, which is at the low end of the expected dosing range. We are pleased to advance this study to the second, higher-dose cohort.”

DTX301 Cohort 1 Data Summary
The 52-week 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, and the pre-defined endpoint for efficacy evaluation occurred 12 weeks after dosing. As of the February 15, 2018 data cutoff date, patient 1 has been followed for 24 weeks, patient 2 for 20 weeks, and patient three for 12 weeks.

Efficacy Summary

The first patient’s rate of ureagenesis was normalized, maintained and then substantially increased over 24 weeks. The rate of ureagenesis at baseline was 67% of normal (200 umol/kg/hr), with the normal rate of ureagenesis defined as 300 umol/kg/hr. The patient had an initial peak effect at 6 weeks at 112% of normal (67% increase from baseline to 335 umol/kg/hr), and then declined at week 12 to 87% of normal (30% increase from baseline to 261 umol/kg/hr,) during the steroid regimen that was used to treat the patient’s mild ALT elevations. After steroids were weaned, ureagenesis began to rebound to 91% of normal at week 20 (36% increase from baseline to 273 umol/kg/hr) and then substantially increased to 134% of normal at week 24 (100.8% increase from baseline to 402 umol/kg/hr). The protocol allows for the tapering or discontinuation of alternate pathway medications and all alternate pathway medications were stopped at week 24 for patient 1 based on their choice. In the 3 weeks since stopping these medications, the patient has been doing well clinically as reported by the investigator.

The second and third patients did not show a clinically meaningful change in rate of ureagenesis over 20 weeks and 12 weeks, respectively.

Safety Summary

As of February 15, 2018 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 the previously-reported 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 as outpatients to treat the ALT elevations and their ALT levels have remained in the normal range (below 40 U/L) since completing the tapering course. The third patient’s ALT levels remained in the normal range through twelve weeks. All three patients have remained clinically and metabolically stable.

DTX301 Cohort 2 Initiation

The Data Monitoring Committee (DMC) has completed its review of the current Cohort 1 data, and Ultragenyx will proceed to the second, higher-dose cohort of the study. Three patients will be enrolled in Cohort 2 and will each receive a single DTX301 dose of 6.0 × 10^12 GC/kg. The first patient is expected to be enrolled in March 2018, and data from the second cohort are expected in the second half of 2018.

About the OTC Phase 1/2 Study (DTX301)
To evaluate therapeutic response of DTX301, the study measures the change in the rate of ureagenesis. Ureagenesis is the process of converting the potent neurotoxin ammonia into urea for excretion, a pathway which is deficient in OTC patients. In the study, the increase in ureagenesis is measured by the conversion of [1-^{13}C] Sodium Acetate to ^{13}C-Urea by the urea cycle. This is accomplished by the oral administration of [1-^{13}C] Sodium Acetate followed by analysis of ^{13}C-Urea in the blood of patients. The Urea Cycle Consortium has also correlated results of the 13C-ureagenesis assay with clinical parameters such as the peak blood ammonia during the presenting metabolic crisis, age of onset and the number of hyperammonemic crises.

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 will 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 is 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 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 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 patients novel products for the treatment of rare and ultra-rare diseases, with a focus on serious, debilitating genetic diseases. Founded in 2010, the company has rapidly built 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 Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 21, 2018, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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

Primary Logo

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