Ultragenyx Announces Positive Topline Cohort 2 Results from Phase 1/2 Clinical Study of DTX301 Gene Therapy in Ornithine Transcarbamylase (OTC) Deficiency and Progression to Higher Dose

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Ureagenesis normalized in one patient in Cohort 2

Cohort 1 responder demonstrated continued biochemical improvement and clinical stability at Week 52

Higher-dose Cohort 3 patient enrollment to begin in 2018; data expected in mid-2019

NOVATO, Calif., Sept. 27, 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 topline positive safety and efficacy data from the second dose cohort and positive longer-term data from the first dose cohort 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.

“Data from the first two dose cohorts continue to demonstrate an acceptable initial safety profile and evidence of clinical activity, with one new patient achieving normalization of ureagenesis in Cohort 2 at 24 weeks,” said Eric Crombez, M.D., Chief Medical Officer of the Ultragenyx Gene Therapy development unit. “The first patient in Cohort 1 with normalized ureagenesis has now completed the initial 52-week study period, and demonstrates a further increased level of ureagenesis at 52 weeks as well as ongoing clinical stability seven months after discontinuing all alternate pathway medication and recent liberalization of a protein-restricted diet.”

DTX301 Cohort 2 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 second dose cohort received a single dose of 6.0 × 10^12 GC/kg. As of the September 12, 2018, data cutoff date, patient 1 in Cohort 2 had been followed for 24 weeks, patient 2 for 21 weeks, and patient 3 for 18 weeks.

Cohort 2 Efficacy Summary

The first patient in Cohort 2 (study patient 4) demonstrated normalization of ureagenesis to 104 percent at Week 24. The patient had an initial peak effect at Week 6 and then a decline at Week 12 that was associated with initiation of a tapering course of steroids to manage a mild asymptomatic elevation in alanine aminotransferase (ALT) levels. After discontinuation of steroids, the rate of ureagenesis normalized at Week 20 and remained normal at Week 24, at which time a second course of steroids had been initiated due to mild asymptomatic ALT elevations, which were controlled.

The second and third patients in Cohort 2 (study patients 5 and 6) did not show a clinically meaningful change in rate of ureagenesis at 12 weeks and did not have ALT elevations nor require steroid treatment.

Safety Summary

As of the cutoff date of September 12, 2018 there have been no infusion-related adverse events and no serious adverse events reported. All adverse events have been Grade 1 or 2. The only treatment-related adverse events in Cohort 2 were the mild, clinically asymptomatic elevations in ALT in the first patient in Cohort 2. These ALT elevations were mild and similar to what has been observed in other programs using AAV gene therapy. All patients have remained clinically and metabolically stable.

Cohort 3 Initiation

The Data Monitoring Committee (DMC) has completed its review of Week 12 data from Cohort 2 and recommended that Ultragenyx proceed to the third dose cohort of the study. In Cohort 3, three patients will be enrolled and will each receive a single dose of 1.0 × 10^13 GC/kg. The first patient is expected to be enrolled before the end of 2018, and data from the Cohort 3 are expected in mid-2019.

About the OTC Phase 1/2 Study (DTX301)
To evaluate the 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 that 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 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 are also evaluated. There are three dose cohorts in the study. Patients in Cohort 1 received a dose of 2.0 × 10^12 GC/kg; patients in Cohort 2 received a dose of 6.0 × 10^12 GC/kg; patients in Cohort 3 will receive a dose of 1.0 × 10^13 GC/kg. The decision to proceed to the next, higher-dose cohort is made after the 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 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 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 approved therapies and product candidates aimed at addressing diseases with high unmet medical need and clear biology for treatment, 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 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 August 3, 2018, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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