Ultragenyx Announces Positive Topline Cohort 3 Results and Improved Longer-Term Cohort 2 Results from Phase 1/2 Study of DTX301 Gene Therapy in Ornithine Transcarbamylase (OTC) Deficiency

January 9, 2020

More uniform response in Cohort 3 with two confirmed responders and one potential responder

New female responder in Cohort 2 for a total of three confirmed female responders across all cohorts

Up to six responders across all nine patients dosed in study

Prophylactic steroid cohort to begin in first half 2020; data expected in second half 2020

Ultragenyx to host conference call today at 4:30 p.m. Eastern Time

NOVATO, Calif., Jan. 09, 2020 (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 Cohort 3 and longer-term data from Cohort 2 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. In Cohort 3 (n=3), there were two confirmed female responders as well a third potential male responder who requires longer-term follow-up to confirm response status. In Cohort 2, one female patient has newly demonstrated a response starting at Week 52 which was confirmed at Week 78. The two previously disclosed responders in Cohort 1 and Cohort 2 also remain clinically and metabolically stable at 104 and 78 weeks, respectively. Across all nine patients dosed in the study, up to six patients have demonstrated a response.

"We are encouraged to see a more uniform response at the higher doses including three female responders. To date, three patients in the study have discontinued alternate pathway medication and liberalized their diets while remaining clinically and metabolically stable," said Eric Crombez, M.D., Chief Medical Officer of the Ultragenyx Gene Therapy development unit. "We are moving to prophylactic steroid use in the next cohort as we believe this could further enhance the level and consistency of expression that we have demonstrated so far."

Cohort 3 Efficacy Summary (as of December 9, 2019 cutoff date): One complete responder, one responder, and one potential responder

Patient 7 (complete responder, female):
Patient 7 demonstrated a clinically meaningful 79 percent change in rate of ureagenesis, from a low of 24 percent of normal at baseline to the 51 to 64 percent range, and staying at 44 percent of normal at Week 52. During this period, she reported feeling significantly better and discontinued her alternate pathway medications and liberalized her protein-restricted diet. She has remained clinically and metabolically stable without a rise in ammonia.

Patient 8 (responder, female):
Patient 8 demonstrated a significant and consistent 90 percent reduction in ammonia levels, time-normalized over a 24 hour period, from a high of 184 umol/L at baseline to 19 umol/L at Week 24, which is within the normal range. Potentially aberrant high baseline ureagenesis values inconsistent with her known more severe clinical status make her ureagenesis results uninterpretable. This patient was on a tapering course of steroids at the time of last assessment and has not yet discontinued alternate pathway medications or liberalized her diet. The investigator reported that her family says her health is the best it has ever been.

Patient 9 (potential responder, male):
Patient 9 showed a 123 percent increase in rate of ureagenesis, from 25 percent of normal at baseline to 56 percent of normal at Week 12 while still on a steroid taper. Steroids have been shown to suppress rate of ureagenesis in other study patients. This patient has not yet discontinued alternate pathway medications or liberalized his diet. His ammonia levels have remained in the normal range and response status will be confirmed after additional follow-up.

Cohort 2 Efficacy Summary: Two responders including new responder and previously-disclosed male complete responder

Patient 6 (new responder, female):
Patient 6 has now shown a 218 percent improvement in rate of ureagenesis, from 20 percent of normal at baseline to 61 percent at Week 52 and maintained at 64 percent at Week 78. In addition, she has shown a significant 74 percent reduction in ammonia levels from 156 umol/L at baseline to 40 umol/L at Week 78. She has started to taper her alternate pathway medications and liberalize her diet. With this new responder, there are two confirmed responders in cohort 2 out of three total patients.

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. All three patients in Cohort 3 had mild, clinically asymptomatic elevations in ALT levels, similar to what has been observed in other programs using AAV-based gene therapy. All three patients have been responding to reactive tapering courses of steroids, and all patients remain clinically stable.

Initiating Prophylactic Steroid Cohort
As previously disclosed, a fourth cohort will enroll three patients at the 1.0 × 10^13 GC/kg dose, using prophylactic steroids. Patients will receive an 8-week tapering regimen of prophylactic steroids, starting at least 5 days prior to dosing with DTX301 at a starting steroid dose of 60 mg/day. The first patient is expected to be enrolled in the first half of 2020, and data from the prophylactic steroid cohort are expected in the second half of 2020.

Potential Phase 3 Study Design
Ultragenyx is continuing discussions with the U.S. Food and Drug Administration (FDA) regarding the potential Phase 3 study design. Ammonia is expected to be a primary endpoint based on direct FDA feedback to date, with ureagenesis as a measure of biologic activity that supports the decision

for patients to discontinue alternate pathway medications.

Conference Call and Webcast Information
Ultragenyx will host a conference call today, Thursday, January 9, 2020, at 4:30 p.m. ET/ 1:30 p.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 ongoing DTX301 Phase 1/2 Study. 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 5583103. The replay of the call will be available for one year.

About the OTC Phase 1/2 Study (DTX301)
The Phase 1/2 study evaluates the change in the rate of ureagenesis, ammonia levels, neurocognitive assessment, biomarkers, and safety of DTX301 in 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 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 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.

Ultragenyx 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 regarding 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 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 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 November 6, 2019, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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