Ultragenyx Announces Positive Data from Phase 1/2 Study of DTX401 Gene Therapy in Glycogen Storage Disease Type Ia

September 4, 2019

Increased Time to Hypoglycemia and Reduction in Cornstarch Use in Cohorts 1 and 2; Improvement of Additional Key Metabolic Measures Observed

Cohort 1 Patients Continue to Demonstrate Long-Term, Durable Responses

Company to Enroll Three Patients in Expansion Cohort to Confirm 6.0 × 10^12 GC/kg Dose as Optimal Dose for Phase 3 Study

Company to Host Conference Call Today at 8:30am ET to Discuss Results

NOVATO, Calif., Sept. 04, 2019 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), a biopharmaceutical company focused on the development of novel products for serious rare and ultra-rare genetic diseases, today announced positive data from the second dose cohort of the ongoing Phase 1/2 study of DTX401, an adeno-associated virus (AAV) based gene therapy for the treatment of glycogen storage disease type Ia (GSDIa). All three patients in Cohort 2 have shown a clinical response with improvements in glucose control and other metabolic parameters compared to baseline. Patients in the first, lower dose cohort continue to show longer-term durability in response. The data were presented today at the Society for the Study of Inborn Errors of Metabolism (SSIEM) 2019 Annual Symposium in Rotterdam, the Netherlands. Based on these results, Ultragenyx will enroll three additional patients into an expansion of cohort 2 at the same 6.0 × 10^12 GC/kg dose to confirm its use in the Phase 3 study.

“Early data from Cohort 2 are promising, with increased week 6 glucose levels and reduced lactate measurements during the controlled fasting challenge indicating a higher level of transgene expression compared to Cohort 1. This is further supported by MRI data indicating better reduction of glycogen storage in the liver,” said Eric Crombez, M.D., Chief Medical Officer of the Ultragenyx Gene Therapy development unit. “Additional assessments of time to hypoglycemia after further weaning off of cornstarch use, combined with the other positive clinical and metabolic data, should support 6.0 × 10^12 GC/kg as the dose for the upcoming Phase 3 study.”

“The response to DTX401 has been better than expected. We have seen all of the patients wean their therapy with some already discontinuing therapy. Missed cornstarch doses no longer are resulting in hypoglycemia which previously could have been life threatening,” said David Weinstein, M.D., M.M.Sc., Professor and Director, Glycogen Storage Disease Program at Connecticut Children’s Medical Center and UConn Health. “The GSD community is extremely excited by the results obtained after the first year of the trial.”

DTX401 Data Summary

Time to Hypoglycemia

All patients have demonstrated a biological and clinical response, reflected by an increase in time to hypoglycemia (defined as glucose <60 mg/dL or onset of clinical symptoms) compared to baseline during a controlled-fasting challenge, including a sustained response through week 52 for the first two patients enrolled. All patients will continue to be followed to evaluate long-term durability of treatment.

Cohort 2 patients showed significant hyperglycemia during the 6 week controlled fasting challenge, which was not observed at baseline and is consistent with a level of transgene expression and glucose release that was more than that observed with Cohort 1. This level of hyperglycemia results in an exaggerated insulin response, which in turn has the potential to drive hypoglycemia and an early termination of the controlled fasting challenge. Nevertheless, all Cohort 2 patients still demonstrated an increase in time to hypoglycemia in the fasting challenge.

	Time to Hypoglycemia (hours)					
	Cohort 1 (2e12 GC/kg)			**Cohort 2 (6e12 GC/kg)**		
Visit	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Baseline	3.8	4.1	5.4	6.1	3.6	3.8
W12	7.7	9.0	6.5	7.2	5.4	6.0 *(+58%)*
W24	6.8	13.1	6.5 *(+20%)*	7.0 *(+15%)*	4.4 *(+22%)*	NR
W52	7.7 *(+103%)*	10.6 *(+159%)*	NR	NR	NR	NR

NR= Not yet reached

Cornstarch Reduction

All patients have demonstrated normalization of daily glucose levels, which has allowed for clinically significant reductions in the amount of cornstarch. Significant cornstarch reduction generally occurred by week 24, and in Cohort 1 where longer-term data are available, cornstarch doses have continued to be titrated down including complete discontinuation of cornstarch for patient 1. Early titration results in Cohort 2 are promising, and titration is expected to continue over time as seen in Cohort 1.

	Cornstarch consumption (grams)					
	Cohort 1 (2e12 GC/kg)			**Cohort 2 (6e12 GC/kg)**		
Visit	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Baseline	405	171	269	325	268	329

W6	355	165	255	270	268	341
W12	160	165	138	265	270	253
W24	94	96	76	100 *(-69%)*	224 *(-16%)*	105*(-68%)**
W52	0 *(-100%)*	76 *(-56%)*	57 *(-79%)*	NR	NR	NR

**Cornstarch level at week 18*

Additional Metabolic Measures
Patients have shown meaningful improvements in additional metabolic and clinical assessments. Patients in Cohort 2 have all demonstrated lower lactate levels after treatment compared to baseline and compared to Cohort 1. All three Cohort 2 patients have also shown consistent early reductions in liver fat fraction (representative of glycogen storage) as measured by MRI at week 12. Cohort 2 patients had significant hyperglycemia during their 6-week controlled fasting challenges. This hyperglycemia may have been exacerbated by the effect of steroids on the steroid-responsive normal promoter of the transgene. This further supports the effect of DTX401 on glucose production and regulation, as GSDIa patients are normally expected to become hypoglycemic during steroid treatment. The cornstarch dose at the beginning of the controlled fasting challenge will be reduced in the future to limit the onset of an insulin spike that can significantly reduce blood sugar, affecting the timed hypoglycemia test.

Safety Summary
As of August 31, 2019, there have been no infusion-related adverse events and no treatment-related serious adverse events reported. All adverse events have been Grade 1 or 2. Four of the six patients in Cohorts 1 and 2 had mild, asymptomatic elevations in alanine aminotransferase (ALT), similar to what has been observed in other programs using AAV-based gene therapy, and were successfully treated with a reactive tapering course of steroids.

DTX401 Expansion Cohort Enrollment Ongoing with Data Expected First Half 2020
Based on these results, Ultragenyx is proceeding to a confirmatory expansion cohort that will enroll three patients at the second cohort dose of 6.0 × 10^12 GC/kg. Data from the expansion cohort are expected in the first half of 2020. If the expansion cohort results are consistent with those observed to date, then the Phase 3 trial expected to begin in 2020 will study this dose level.

DTX401 Phase 1/2 Study Design
The open-label, multicenter Phase 1/2 study is evaluating the safety, tolerability and therapeutic response of DTX401 in adults with GSDIa. DTX401 is an AAV8 expressing the glucose-6-phosphatase gene (G6Pase-α) under control of the native promoter. In the first cohort, three patients received a single 2.0 × 10^12 GC/kg dose of DTX401. In the second cohort, three patients each received a single 6.0 × 10^12 GC/kg dose of DTX401. In the expansion cohort, three patients will receive the same dose of DTX401 as in Cohort 2. Key efficacy assessments include time to hypoglycemia (defined as glucose <60 mg/dL or onset of clinical symptoms) during a controlled in-hospital fasting challenge, cornstarch reduction, impact on biomarkers such as lactic acid, and measurement of glycogen storage in liver by MRI.

About GSDIa
GSDIa is the most severe genetically inherited glycogen storage disease. It is caused by a defective gene for the enzyme G6Pase-α, resulting in the inability to regulate blood sugar (glucose). Hypoglycemia in patients with GSDIa can be life-threatening, while the accumulation of the complex sugar glycogen in certain organs and tissues can impair the ability of these tissues to function normally. If chronically untreated, patients can develop severe lactic acidosis, progress to renal failure, and potentially die in infancy or childhood. There are no approved pharmacologic therapies. An estimated 6,000 patients worldwide are affected by GSDIa.

About DTX401

DTX401 is an investigational AAV8 gene therapy designed to deliver stable expression and activity of G6Pase-α under control of the native promoter. DTX401 is administered as a single intravenous infusion and has been shown in preclinical studies to improve G6Pase-α activity and reduce hepatic glycogen levels, a well-described biomarker of disease progression. DTX401 has been granted Orphan Drug Designation in both the United States and Europe, Regenerative Medicine Advanced Therapy (RMAT) designation and Fast Track designation in the United States.

Conference Call Details

Ultragenyx will host a conference call today, Wednesday, September 4 at 8:30 am ET during which Dr. Kakkis and Dr. Weinstein will discuss results of the data being presented at the SSIEM Conference. The live and replayed webcast of the call 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 5648479. The replay of the call will be available for one year.

About Ultragenyx Pharmaceutical, Inc.
Ultragenyx is a biopharmaceutical company committed to bringing 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 filed on Form 10-Q with the Securities and Exchange

Commission on August 2, 2019, and its subsequent periodic reports filed with the Securities and Exchange Commission.

Contact Ultragenyx Pharmaceutical Inc.

Investors & Media
Danielle Keatley
415-475-6876

Source: Ultragenyx Pharmaceutical Inc.