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Ultragenyx Reports Positive Interim Data from Pediatric and Adult Phase 2 Studies of KRN23 in X-Linked Hypophosphatemia

Pediatric study demonstrates substantial reduction in bone disease and improvement in growth

Adult study demonstrates increase in serum phosphorus and provides evidence of clinical improvement

Company to host conference call today at 11am ET to discuss results

NOVATO, Calif., Sept. 19, 2016 (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 data from the ongoing pediatric Phase 2 study of KRN23 for the treatment of X-linked hypophosphatemia (XLH), demonstrating that serum phosphorus levels, rickets, growth rates and other functional outcomes improved with continued KRN23 treatment. The bi-weekly dose regimen continued to show a better overall response than patients who were dosed every four weeks, and patients with higher rickets at baseline showed greater improvements in bone disease and growth velocity. Data were also presented from the adult Phase 2 study of KRN23 for the treatment of XLH, demonstrating a significant increase in serum phosphorus levels and evidence of clinical improvement in walking, mobility, pain and stiffness at 24 weeks of treatment. Adverse events were consistent with what has been previously observed for KRN23 for the treatment of XLH. Ultragenyx is conducting the program under a collaboration and license agreement with Kyowa Hakko Kirin to develop and commercialize KRN23. Data from the two studies were presented today at the American Society for Bone and Mineral Research (ASBMR) 2016 Annual Meeting.

"Patients with XLH suffer from substantial bone disease, pain and stiffness throughout the entire course of their lives," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "These data support the potential for KRN23 to treat XLH in both pediatric and adult patients, who all experience significant burden of disease and are in need of new treatment options."

"The accrued data from the ongoing KRN23 trials in children affected with XLH provide encouraging expectations for improving therapeutic outcomes in this condition," commented Tom Carpenter, M.D., the lead investigator in this study. "It has become more evident that the responses to KRN23 therapy observed in patients have the potential to transform the treatment of XLH."

Phase 2 Pediatric Study

The randomized, multicenter, open-label, dose finding study enrolled 52 patients ages five through 12, 49 of whom had been on currently available therapy (oral phosphate/active Vitamin D therapy) for an average of approximately seven years prior to entering the study. The first 36 patients enrolled in the study have completed the full 64-week dose-titration and treatment period. A subset of these patients (n=18) were pre-specified as having higher rickets (greater bone disease), defined by baseline total RSS scores of $\geq$ 1.5. An additional 16 patients with higher rickets have completed 40 weeks of treatment.

Metabolic Measures

Patients demonstrated increases in mean serum phosphorus, renal phosphate reabsorption (TmP/GFR) and serum 1,25 dihydroxy vitamin D levels through 64 weeks of treatment. Patients in both dosing groups had mean serum phosphorus levels in the low normal range through 64 weeks of treatment, demonstrating that phosphate wasting, the underlying cause of the disease, improved and patients were able to maintain increased serum phosphorus levels.

Bone Disease Results

Thacher Rickets Severity Scoring (RSS)

Rickets severity was assessed at 40 weeks (n=52) and 64 weeks (n=36) using the RSS scoring system. Rickets improved

significantly in all groups, with the greatest improvements in patients with higher baseline rickets (RSS ≥1.5) who received bi-weekly dosing of KRN23.

52 patients/40 weeks	**Q2W**	**Overall**		**Q2W**	**Overall**
RSS, All Patients			***RSS, Higher BL RSS ≥ 1.5***		
n	26	52	n	17	34
% reduction (p < 0.0001)	61%	50%	% reduction (p < 0.0001)	71%	61%
36 patients/64 weeks					
RSS, All Patients			***RSS, Higher BL RSS ≥ 1.5***		
n	18	36	n	9	18
% reduction (p < 0.0001)	51%	38%	% reduction (p < 0.0001)	57%	51%

Radiographic Global Impression of Change (RGI-C) Scale

The change in the severity of rickets was also assessed at 40 and 64 weeks by the RGI-C score. Data show significant improvement in rickets in all groups. Substantial healing (RGIC score $\geq$ 2) was observed in all but one patient with higher baseline rickets who received bi-weekly dosing.

52 patients/40 weeks	**Q2W**	**Overall**		**Q2W**	**Overall**
RGI-C, All Patients			***RGI-C, Higher BL RSS ≥ 1.5***		
n	26	52	n	17	34
Score change (p < 0.0001)	1.72	1.56	Score change (p < 0.0001)	2.04	1.91
36 patients/64 weeks					
RCI-C, All Patients			***RGI-C, Higher BL RSS ≥ 1.5***		
n	18	36	n	9	18
Score change (p < 0.0001)	1.35	1.35	Score change (p < 0.0001)	1.96	1.91

Growth Velocity

Patients with higher baseline RSS scores $\geq$ 1.5 showed more growth impairment (baseline height percentile for 40-week group = 5.8%; baseline height percentile for 64-week group = 3.9%), and these patients demonstrated greater improvement in growth velocity and height z-score.

52 patients/40 weeks	**Q2W**	**Overall**		**Q2W**	**Overall**
Growth, All Patients			***Growth, Higher BL RSS ≥ 1.5***		
n	26	52	n	17	34
Growth velocity change (cm/yr)	+0.96	+0.68	Change in growth velocity (cm/yr)	+1.69	+1.23
p value	0.0088	0.0321	p value	<0.0001	0.0046
Change in height z-score	0.17	0.13	Change in height z-score	0.22	0.18
p value	<0.0001	<0.0001	p value	<0.0001	0.0003
36 patients/64 weeks					
Growth, All Patients			***Growth, Higher BL RSS ≥ 1.5***		
n	18	36	n	9	18
Growth velocity change (cm/yr)	+0.35	+0.27	Change in growth velocity (cm/yr)	+0.74	+0.58
p value	N.S.	N.S.	p value	0.0173	0.023
Change in height z-score	0.21	0.16	Change in height z-score	0.21	0.19
p value	<0.0001	<0.0001	p value	0.0056	0.0002

Functional Measurements: 6 Minute Walk Test (6MWT) and Patient Reported Outcomes (PROs)

Patients with walking impairment at baseline (defined by < 80% predicted normal walk distance in 6MWT) in the bi-weekly dosing group achieved a mean increase of 84 meters (p<0.001) at 40 weeks (n=14), and 97 meters (p<0.001) at 64 weeks (n=7).

Functional disability scores were measured with the Pediatric Orthopedic Society North America/Pediatric Outcome Data Collection Instrument (POSNA/PODCI). When evaluating the Global score of all five domains in those patients with substantial impairment at baseline (n=28, defined as baseline scores < 40 or one standard deviation below the normalized score of 50), a mean improvement of +17.5 (p< 0.0001) was observed at 40 weeks. Though the magnitude of these changes in functional measurements are substantial, any conclusions must be tempered by the fact that these data are from an uncontrolled, open-label study.

Safety and Tolerability

The most common treatment-related adverse events reported by preferred term was injection site reaction in 33% of patients. All of these reactions were considered mild. All other treatment-related adverse events were also considered mild. There was one serious adverse event considered possibly treatment-related. This was a previously reported patient with fever and muscle pain who improved without complication and is still in the trial. There have been no deaths or discontinuations from the study for any reason. No clinically meaningful changes were observed in mean serum calcium, urinary calcium and in serum intact parathyroid hormone. None of the patients had serum phosphorus levels above the upper limit of normal at any time point. No clinically significant changes were observed in renal ultrasounds pre- and post-treatment.

Phase 2 Adult Extension Study

The open-label, long-term extension study enrolled 20 adult patients with XLH who had previously participated in the phase 1 INT-001 or INT-002 studies of KRN23. All patients had at least a 12-month KRN23 treatment break before enrolling in the extension study. Patients who had resumed oral phosphate and active vitamin D therapy between studies (65%) completed a 21-day washout period. All patients began KRN23 treatment at the last dose received in the INT-001 or 002 study with an option to titrate during the first 12 weeks. An analysis of 24-week data is being presented.

Metabolic Measures

Patients treated with KRN23 demonstrated increased serum phosphorus at 24 weeks of treatment, and maintained levels in the low normal range. Renal phosphate reabsorption (TmP/GFR) and serum 1,25 dihydroxy vitamin D levels also increased from baseline to 24 weeks.

Patient-Reported Outcomes and Physical Function

At baseline, 19 of 20 patients had worst pain scores measured by the Brief Pain Inventory Question 3 (BPI-Q3) of $\geq$ 4, classified as moderate to severe pain. The mean BPI-Q3 score was significantly reduced from baseline (p=0.0268; 1.1 point reduction from 6.6 at baseline to 5.5 at 24 weeks). These patients also demonstrated significant improvements in BPI pain interference (p=0.0009) and pain severity (p=0.0141) scores.

WOMAC pain, stiffness and physical function domain scores were significantly reduced at 24 weeks in these patients. Patients demonstrating the greatest improvements in stiffness (WOMAC stiffness responders) and pain (BPI-SF worst pain responders) had greater improvements in mobility tests, including the Timed Up and Go (TUG test for balance and agility) and the 6MWT. Mean patient TUG scores improved by 2 seconds (p=0.04) at week 24. At baseline, nearly all patients (19/20) were impaired in walking (defined by < 80% predicted normal walk distance in 6MWT). The mean increase in distance walked was 25 meters (p=0.05) from baseline.

Safety and Tolerability

The most common adverse events were arthralgia (30%), nasopharyngitis (25%), back pain (20%), injection site reaction (20%), and pain in extremity (20%). Treatment-related adverse events occurred in 40% of patients, and were all considered mild. None of the four serious adverse events were considered treatment-related. There have been no deaths or discontinuations from the study.

Conference Call Details

Ultragenyx will host a conference call on Monday, September 19 at 11am ET during which Dr. Kakkis will discuss results of the KRN23 studies being presented at the ASBMR Annual Meeting. 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 83882106. The replay of the call will be available for one year.

About XLH

XLH is a disorder of phosphate metabolism caused by phosphate wasting in the urine leading to severe hypophosphatemia. XLH is the most common heritable form of rickets (the softening and weakening of bones), that is inherited as an X-linked dominant trait affecting both males and females. XLH is a distinctive disease characterized by inadequate mineralization of bone that leads to a spectrum of abnormalities, including rickets, progressive bowing of the leg, osteomalacia, bone pain, waddling gait, short stature, gross motor impairment, muscle weakness, frequent/poorly healing pseudofractures, spinal stenosis, enthesopathy, and osteoarthritis. Most pediatric patients and some adult patients are managed using oral phosphate replacement and active vitamin D (calcitriol) therapy, which requires multiple divided doses each day and monitoring for potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism.

About KRN23

KRN23 is an investigational recombinant fully human monoclonal IgG_1 antibody, discovered by Kyowa Hakko Kirin, against the phosphaturic hormone fibroblast growth factor 23 (FGF23). It is being developed by Ultragenyx and Kyowa Hakko Kirin to treat XLH and TIO, diseases characterized by excess activity of FGF23. FGF23 is a hormone that reduces serum levels of phosphorus and active vitamin D by regulating phosphate excretion and active vitamin D production by the kidney. Phosphate wasting in XLH and TIO is caused by excessive levels and activity of FGF23. KRN23 is designed to bind to and thereby inhibit the excessive biological activity of FGF23. By blocking excess FGF23 in patients with XLH and TIO, KRN23 is intended to increase phosphate reabsorption from the kidney and increase the production of vitamin D, which enhances intestinal absorption of phosphate and calcium.

A Phase 3 program studying KRN23 in adults and a Phase 2 study in pediatric patients with XLH are ongoing. KRN23 is also being developed for tumor-induced osteomalacia (TIO), a disease characterized by typically benign tumors that produce excess levels of FGF23, which can lead to severe osteomalacia, fractures, bone and muscle pain, and muscle weakness.

About Ultragenyx

Ultragenyx is a clinical-stage 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. 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.

About Kyowa Hakko Kirin

Kyowa Hakko Kirin is a leading biopharmaceutical company in Japan focusing on its core business area of oncology, nephrology, and immunology/allergy. Kyowa Hakko Kirin leverages antibody-related leading-edge technologies to discover and develop innovative new drugs aiming to become a global specialty pharmaceutical company which contributes to the health and well-being of people around the world.

For more information, please visit www.kyowa-kirin.com.

Forward-Looking Statements

Except for the historical information contained herein, the matters set forth in this press release, including statements regarding Ultragenyx's expectations regarding the timing of release of additional data for its product candidates, plans to initiate additional studies for its product candidates and timing regarding these studies, plans regarding ongoing studies for existing programs and its intent to file for conditional approval, 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, including the regulatory approval process, the timing of our regulatory filings, and other matters that could affect the success of our drug

development programs, including KRN23. 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 the Company in general, see Ultragenyx's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on August 9, 2016, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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