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Ultragenyx Releases Positive 16-Week Interim Data From Pediatric Phase 2 Study of KRN23 in X-Linked Hypophosphatemia

Potential conditional approval pathway in Europe

Phase 3 adult XLH program initiation expected in 2H 2015

NOVATO, Calif., June 2, 2015 (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 16-week data from the ongoing pediatric Phase 2 study and provided a regulatory update for its recombinant human monoclonal antibody KRN23 against fibroblast growth factor 23 (FGF23) for the treatment of X-linked hypophosphatemia (XLH). XLH is an inherited metabolic bone disease characterized by short stature, skeletal deformities, bone pain, fractures, and muscle weakness. Ultragenyx and Kyowa Hakko Kirin entered into a collaboration and license agreement in August 2013 to develop and commercialize KRN23.

Positive Interim Safety and Efficacy Data from Phase 2 Study in Pediatric XLH Patients

After 16 weeks of dose-titration, all 36 patients had increases in serum phosphorus levels from baseline. In the monthly dosing group, mean serum phosphorus at peak increased by 1.03 mg/dL, from 2.27 mg/dL at baseline to 3.30 mg/dL, which is in the normal range (3.2-6.1 mg/dL). At the end of the 16-week titration period, 71% of patients receiving monthly dosing reached the normal serum phosphorus range with a mean dose of 0.84 mg/kg per treatment. Of the patients who had reached week 22, 9 out of 12 (75%) reached the normal range after further dose titration.

In the biweekly dosing group, mean serum phosphorus increased by 0.59 mg/dL, from 2.48 mg/dL at baseline to 3.07 mg/dL, and was stable throughout the dosing cycle. The proportion of patients reaching the normal serum phosphorus range was 50% at the end of 16 weeks with a mean dose of 0.48 mg/kg per treatment biweekly. Of the patients who had reached week 24, 7 out of 9 (78%) reached the normal range after further dose titration.

Mean increases were also observed in renal phosphate reabsorption (TmP/GFR) and in serum 1,25 dihydroxy vitamin D levels. Overall, the dose-response, serum phosphorus, and other metabolite results observed in the pediatric study are consistent with the adult XLH data generated to date.

"The 16-week data from the Phase 2 study in pediatric XLH patients corroborates the Phase 1/2 data in adults demonstrating increases in serum phosphorus in all patients and a favorable safety and tolerability profile," commented Sunil Agarwal, M.D., Chief Medical Officer of Ultragenyx. "Based on the positive data and productive discussions with the U.S. and European regulatory agencies we are expanding our Phase 2 pediatric study and moving ahead with a Phase 3 program in adults."

Serum phosphorus levels on standard of care

Per protocol, patients discontinued standard of care (SOC: oral phosphate and Vitamin D therapy) after the screening visit, which was 2-4 weeks prior to the baseline visit. Serum phosphorus levels were measured in 16 patients at screening and baseline. While on SOC, the mean serum phosphorus level at screening in these 16 patients was 2.40 mg/dL and after wash-out from SOC at baseline was 2.26 mg/dL, representing a mean change of 0.14 mg/dL. All 16 patients had an increase in serum phosphorus after treatment with KRN23 to a mean of 3.09 mg/dL, representing an improvement of 0.83 mg/dL compared to baseline.

Safety and tolerability

No serious adverse events have been reported and there have been no discontinuations from the pediatric Phase 2 study for any reason. The most common adverse events considered to be treatment related were injection site reactions in 8 patients (22%), injection site erythema in 4 patients (11%), and injection site rash, injection site swelling, and limb pain in 3 patients (8% each). All of these treatment-related adverse events were considered mild in severity.

No significant changes were observed in serum calcium, urinary calcium, or serum intact parathyroid hormone (iPTH). No

patients had serum phosphorus levels above the upper limit of normal in either dosing group.

Potential Conditional Approval Pathway in Europe

In recent discussions with the European Medicines Agency (EMA), Ultragenyx received feedback that a Marketing Authorization Application (MAA) filing for conditional approval may be possible for KRN23 in XLH. A conditional MAA filing would be based on data from the 40-week interim analysis of rickets and other endpoints from the pediatric Phase 2 study and from the completed Phase 1/2 and ongoing Phase 2b studies in adults, provided that there is a positive benefit-risk profile, with specific obligations to complete and provide final data from the pediatric and adult studies. If KRN23 is approved, Kyowa Hakko Kirin will commercialize it in Europe, and Ultragenyx will receive a royalty.

Based on the positive 16-week results and the EMA feedback, Ultragenyx is expanding the pediatric Phase 2 study by up to 16 patients to generate additional safety and efficacy data. The company will determine whether to proceed with an MAA filing for conditional approval after evaluation of the Phase 2 40-week data from the original 36 patients and again, if necessary, data from the fully expanded study. The data analysis at 40 weeks, which will include radiographic evidence of rickets, is expected in late 2015 or early 2016 for the original 36 patients and mid-2016 for all patients.

Adult Phase 3 Program Expected to Begin in the Second Half of 2015

Based on discussions with the EMA and U.S. Food and Drug Administration (FDA), the company plans to initiate a Phase 3 randomized, double-blind, placebo-controlled study in approximately 120 adult patients with XLH. The study will include a 24-week blinded period followed by a 24-week open-label cross-over period. The planned primary endpoint will be serum phosphorus levels at 24 weeks. The Brief Pain Inventory (BPI) patient-reported outcome will be a key secondary endpoint. The study will also evaluate biomarkers of bone remodeling, physical function, and other patient-reported outcomes. Ultragenyx also plans to initiate a 48-week open-label bone quality study in approximately ten adult XLH patients evaluating the impact of KRN23 on underlying osteomalacia via bone biopsy. Both studies are expected to start in the second half of 2015.

About X-Linked Hypophosphatemia (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 that is inherited as an X-linked dominant trait affecting both males and females, though some reports indicate that the disease may be more severe in males. XLH is a distinctive bone 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 vitamin D (calcitriol) therapy, which requires frequent divided doses and careful medical monitoring. It is partially effective at reducing rickets in pediatric patients, but it does not improve growth and can be challenging to optimize the dose without increasing the risk of depositing phosphate-calcium precipitates in the kidneys (nephrocalcinosis).

Phase 2 Study Design

The randomized, open-label, dose-finding Phase 2 study is evaluating safety and efficacy in 36 pediatric XLH patients ages 5 to 12. The study consists of a 16-week individual dose-titration period followed by a 48-week treatment period, for a total of 64 weeks. Patients are divided into three cohorts of escalating starting dose levels of KRN23 with either monthly (Q4W) or biweekly (Q2W) dosing regimens. Patients can continue to have their dose increased throughout the duration of the study to reach an individually-optimized dose.

Safety, changes in serum phosphorus, and other pharmacodynamic parameters were evaluated at the 16-week analysis. Additional data, including radiographic evidence of rickets severity, will be evaluated at the 40-week and 64-week analyses.

About KRN23 and FGF23

KRN23 is an investigational recombinant fully human monoclonal IgG₁ antibody, discovered by Kyowa Hakko Kirin, against the phosphaturic hormone fibroblast growth factor 23 (FGF23). It is being developed by Ultragenyx to treat XLH, a disease characterized by excess activity of FGF23. FGF23 is a hormone that reduces serum levels of phosphorus and vitamin D by regulating phosphate excretion and vitamin D production by the kidney. Phosphate wasting in XLH 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, KRN23 is intended to restore normal phosphate reabsorption from the kidney and increase the production of vitamin D, which enhances intestinal absorption of phosphate and calcium.

Multiple clinical studies of KRN23 in adult patients with XLH have been completed and Ultragenyx intends to continue development of KRN23 in adults with XLH. In addition, a Phase 2 study in pediatric patients with XLH is 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 biotechnology 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 a potential Marketing Authorization Application filing for conditional approval, timing of release of additional data, plans regarding a Phase 3 study and the likelihood of obtaining full approval in Europe and the U.S. and the expected timing of initiation of additional 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, including the regulatory approval process, the timing of our regulatory filings, and other matters that could affect 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 the Company in general, see Ultragenyx's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on May 11, 2015, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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