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Ultragenyx Releases Positive Interim 40-Week Bone Treatment Data From Ongoing Pediatric Phase 2 Study of KRN23 in X-Linked Hypophosphatemia

8 of 11 Patients Showed Improvement in Rickets Bone Disease, Including 5 of 5 in Biweekly Dosing Group

NOVATO, Calif., July 9, 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 interim data from the first 12 patients in the ongoing pediatric Phase 2 study for its recombinant human monoclonal antibody KRN23 against fibroblast growth factor 23 (FGF23) for the treatment of X-linked hypophosphatemia (XLH). An improvement in mean rickets score was observed after 40 weeks of treatment with investigational KRN23 in these patients. Ultragenyx is conducting the Phase 2 study under a collaboration and license agreement with Kyowa Hakko Kirin to develop and commercialize KRN23.

Bone Disease Efficacy

Eleven of the first 12 patients enrolled had been on standard of care oral phosphate/Vitamin D therapy for an average of 6 years (3.3-9.4 years) prior to the baseline assessment. The mean rickets score was 1.4 at baseline using the Thacher Rickets Severity Scoring method as evaluated by a blinded expert reader and decreased to 0.6 after 40 weeks of treatment with KRN23, a 58% reduction. Eight out of 11 patients with rickets at baseline demonstrated an improvement in rickets, of which three patients no longer exhibited radiographic evidence of rickets at week 40. One patient in the biweekly dosing group did not present with radiographic evidence of rickets at baseline and was excluded from the analysis.

Of the 12 patients, 6 received biweekly dosing and 6 received monthly dosing of KRN23. Of the 5 patients with rickets at baseline in the biweekly dosing group, 100% demonstrated improvement in rickets from a mean baseline rickets score of 1.5 to a mean score of 0.3 at week 40, representing an 80% reduction in rickets score. Of the 6 patients in the monthly dosing group, 50% demonstrated improvement in rickets from a mean baseline score of 1.3 to a mean score of 0.8 at week 40, representing a 38% reduction in rickets score. Two patients in the monthly dosing group did not show a change and one patient in the monthly dosing group worsened by 0.5 points.

"These interim data are encouraging as they are the first indication that KRN23 may improve rickets beyond what can be achieved with standard of care," commented Sunil Agarwal, M.D., Chief Medical Officer of Ultragenyx. "We look forward to discussing these data with the U.S. and European Union regulatory agencies to determine appropriate next steps for the pediatric development program."

Metabolic Measures

In the biweekly dosing group (n=6), mean serum phosphorus increased by 0.70 mg/dL, from 2.78 mg/dL at baseline to 3.48 mg/dL, which is in the normal range (3.2-6.1 mg/dL). In the monthly dosing group (n=6), mean serum phosphorus at peak increased by 1.06 mg/dL, from 2.42 mg/dL at baseline to 3.48 mg/dL. The monthly dosing patients showed a decrease to the trough level before the next dose, unlike the biweekly regimen which showed stable phosphate levels.

Increases in renal phosphate reabsorption (TmP/GFR) and in serum 1,25 dihydroxy vitamin D levels were observed in all 12 patients.

Safety and Tolerability

No serious adverse events have been reported in the study to date and there have been no discontinuations from the study for any reason. For the 12 patients who had reached 40 weeks at the time of the interim analysis, the most common adverse events considered to be treatment related were injection site reactions. All of the 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) in the 12 patients. None of the patients had serum phosphorus levels above the upper limit of normal in either dosing group. Safety data on renal ultrasounds, echocardiograms, or immune response to KRN23 are not yet available.

All patients in the study continue to receive KRN23. An additional 40-week analysis for 36 patients is planned for the fourth quarter of 2015.

FDA Fast Track Designation

Ultragenyx also announced that the U.S. Food and Drug Administration (FDA) has granted Fast Track Designation to the KRN23 program in XLH. Fast Track Designation is intended to facilitate the development and expedite the review of drugs for serious and life-threatening conditions that have the potential to address an unmet medical need. The designation allows for more frequent interaction with the FDA review team. It also enables eligibility for priority review and the potential for a rolling review of the Biologics License Application, when and if filed.

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 (the softening and weakening of bones) 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 approximately 50 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 or biweekly dosing regimens. Patients can continue to have their dose increased throughout the duration of the study to reach an individually-optimized dose.

The evaluation of rickets in the study is done via radiographs of the wrists and knees. The scoring was done using the Thacher Rickets Severity Score, a pre-specified 10-point scale that measures knee and wrist irregularities. Each radiograph is scored by one central independent reviewer who is blinded to the subject's adherence, dose, dose regimen, and radiographic sequence.

Safety, changes in serum phosphorus, and other pharmacodynamic parameters were evaluated at the 16-week analysis. The current interim analysis includes the first 12 patients enrolled in the study by the lead investigator Thomas Carpenter, M.D. Additional safety, tolerability, and efficacy data, including radiographic evidence of rickets severity, will be evaluated for all patients 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 timing of release of additional data and analysis of same, discussions with regulatory authorities, and the potential benefits of Fast Track Designation, 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 12, 2015, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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