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Ultragenyx, Kyowa Hakko Kirin and Kyowa Kirin International Announce Positive 24-Week Data from Adult Phase 3 Study of Burosumab (KRN23) in X-Linked Hypophosphatemia

Study met primary endpoint of serum phosphorus response and key secondary endpoint of stiffness improvement

Ultragenyx to host conference call today at 4:30pm ET to discuss results

NOVATO, Calif., LONDON and TOKYO, April 18, 2017 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), Kyowa Hakko Kirin Co., Ltd. (Kyowa Hakko Kirin) and Kyowa Kirin International PLC, a wholly owned subsidiary of Kyowa Hakko Kirin, today announced positive 24-week data from the randomized, double-blind, placebo-controlled Phase 3 study of burosumab (KRN23) in adults with X-linked hypophosphatemia (XLH). Patients treated with burosumab demonstrated a statistically significant improvement in serum phosphorus levels, with 94% of patients achieving normal levels compared to 8% on placebo ($p<0.0001$). Patients treated with burosumab also achieved a statistically significant improvement in stiffness and strong trends in improvements in physical function and pain. Adverse events were consistent with what has been previously observed in open label studies in adults and children. Ultragenyx is conducting the study under a collaboration and license agreement with Kyowa Hakko Kirin. Burosumab is being developed by Ultragenyx, Kyowa Hakko Kirin and Kyowa Kirin International.

"These data demonstrate a clinical improvement in patients treated with burosumab and support the potential for treatment of adults," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "When combined with a favorable safety profile and a strong serum phosphorus response, we believe these clinical data should support regulatory submissions in adults with XLH, and we look forward to discussing our filing plans with the U.S. FDA."

"This study provides valuable additional placebo controlled data to that already obtained from the global clinical development program for pediatric and adult patients with XLH." said Mitsuo Satoh, Executive Officer, Vice President, Head of Research and Development Division of Kyowa Hakko Kirin. "I believe burosumab has the potential to be an effective treatment option for patients with XLH."

"We are pleased that the data from this adult Phase 3 study supports the safety and efficacy of burosumab and look forward to progressing our discussions with the regulatory bodies in Europe and the US," said Dr. Tom Stratford, President and CEO of KKI.

Efficacy Results

The study enrolled 134 patients, randomized 1:1 to burosumab at a dose of 1 mg/kg or placebo every four weeks for 24 weeks. The study met the primary endpoint of increasing serum phosphorus levels as 94% of patients treated with burosumab (n=68) achieved serum phosphorus levels above the lower limit of normal and maintained levels in the low normal range through 24 weeks, compared to 8% in the placebo arm (n=66; $p<0.0001$).

There were three pre-specified key secondary endpoints, including stiffness and physical function, both measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®), and pain measured by the Brief Pain Inventory Question 3 (BPI Q3; pain at its worst in the last 24 hours). At week 24 stiffness improved by a mean score of 7.87 points for patients treated with burosumab compared to a 0.25 point worsening among patients in the placebo group (mean difference of 8.12; $p=0.0122$). Physical function improved by 3.11 points for patients treated with burosumab compared to a 1.79 point worsening among patients in the placebo group (mean difference of 4.90 points; $p=0.0478$). Pain score improved by 0.79 for patients treated with burosumab compared to a 0.32 improvement among patients in the placebo group (mean score difference of 0.46 points; $p=0.0919$). Results were directionally consistent towards improvement across all three key secondary endpoints. After pre-planned multiplicity adjustment, the improvement in stiffness among patients treated with burosumab remained statistically significant at the less than the 0.0167 threshold, while physical function and pain scores demonstrated strong trends.

Safety Results

There was no difference in the overall frequency of treatment emergent adverse events, treatment related adverse events and serious adverse events between the two treatment groups. The most common (≥10%) adverse events in patients treated with either burosumab or placebo were back pain (burosumab 15%, placebo 9%), nasopharyngitis (burosumab 13%, placebo 9%), tooth abscess (burosumab 13%, placebo 8%), injection site reactions (burosumab 12%, placebo 12%), headache (burosumab 12%, placebo 8%), restless legs syndrome (burosumab 12%, placebo 8%), dizziness (burosumab 10%, placebo 6%), nausea (burosumab 10%, placebo 9%), arthralgia (burosumab 9%, placebo 24%), pain in extremity (burosumab 7%, placebo 15%) and oropharyngeal pain (burosumab 2%, placebo 11%). There was no evidence of hypersensitivity reactions to injections. There were two serious adverse events in each treatment group, none of which were considered treatment-related. No differences between groups were observed in serum intact parathyroid hormone levels or ectopic mineralization as assessed by renal ultrasounds or echocardiograms.

Of the 134 patients enrolled in the study, one patient in the burosumab arm discontinued treatment during the 24-week double-blind treatment period due to consent withdrawal. There have been no deaths in the study.

About the Phase 3 Adult XLH Program

This Phase 3 study is a randomized, double-blind, placebo-controlled clinical study designed to assess the efficacy and safety of burosumab administered every four weeks in 134 adult XLH patients in the US, EU, Canada, Japan, and Korea. The primary endpoint of the study is the percentage of patients who achieved average serum phosphorus levels in the normal range over 24 weeks. The three key secondary endpoints are pain measured by BPI Q3, stiffness and physical function, both measured by WOMAC®. After 24 weeks, all patients receive burosumab through the extension period of the study.

Ultragenyx is conducting a second, fully-enrolled open-label bone quality Phase 3 study in 14 adult XLH patients evaluating the improvement in osteomalacia, the underlying bone pathology of XLH, via bone biopsy. The bone quality study complements the phosphate and patient symptom data from the larger Phase 3 XLH study by evaluating the effect of burosumab more directly on the bone.

About Burosumab (KRN23)

Burosumab is an investigational recombinant fully human monoclonal IgG_1 antibody, discovered by Kyowa Hakko Kirin, against the phosphaturic hormone fibroblast growth factor 23 (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. Burosumab is being developed by Ultragenyx and Kyowa Hakko Kirin to treat XLH and tumor-induced osteomalacia (TIO), diseases characterized by excess levels of FGF23. Phosphate wasting in XLH and TIO is caused by excessive levels and activity of FGF23. Burosumab is designed to bind to and thereby inhibit the biological activity of FGF23. By blocking excess FGF23 in patients with XLH and TIO, burosumab 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 clinical program studying burosumab in adults and pediatric patients with XLH is ongoing. Burosumab is also being developed for 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.

Details of Ultragenyx Conference Call

Ultragenyx will host a conference call today, Tuesday, April 18, 2017 at 4:30pm ET, during which Dr. Kakkis will discuss the topline data. 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 10146009. The replay of the call will be available for one year.

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 Kirin

Kyowa Hakko Kirin Co., Ltd. is a research-based life sciences company, with special strengths in biotechnologies. In the core therapeutic areas of oncology, nephrology and immunology/allergy, Kyowa Hakko Kirin leverages leading-edge biotechnologies centered on antibody technologies, to continually discover innovative new drugs and to develop and market those drugs world-wide. In this way, the company is working to realize its vision of becoming a Japan-based global specialty pharmaceutical company that contributes to the health and wellbeing of people around the world.

Kyowa Kirin International PLC (KKI) is a wholly owned subsidiary of Kyowa Hakko Kirin and is a rapidly growing specialty pharmaceutical company engaged in the development and commercialisation of prescription medicines for the treatment of unmet therapeutic needs in Europe and the United States. KKI is headquartered in Scotland.

You can learn more about the business at: 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 ongoing or additional studies for its product candidates and timing regarding these studies, potential indications for its product candidates, discussions with the FDA and sufficiency for, 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, 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, such as the regulatory approval process, the timing of our regulatory filings 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 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 Annual Report on Form 10-K filed with the Securities and Exchange Commission on February 17, 2017, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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