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Ultragenyx and Kyowa Kirin Announce Positive 48-Week Data from Adult Phase 3 Study of Burosumab (KRN23) in X-Linked Hypophosphatemia

Further improvement in disease symptoms and fracture healing observed through 48 weeks of treatment with burosumab

NOVATO, Calif. and TOKYO and LONDON, Dec. 04, 2017 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), a biopharmaceutical company focused on the development of novel products for rare and ultra-rare diseases, Kyowa Hakko Kirin Co., Ltd. (Kyowa Hakko Kirin) and Kyowa Kirin International PLC (Kyowa Kirin International) today announced positive 48-week data from the randomized, double-blind, placebo-controlled Phase 3 study of burosumab (KRN23) in adults with X-linked hypophosphatemia (XLH). Treatment with burosumab for 48 weeks showed sustained maintenance of normal serum phosphorus levels and further improvement in stiffness, physical function and pain. Patients who crossed over from placebo to burosumab after 24 weeks showed normalization of serum phosphorus and improvement in stiffness, pain and physical functioning. An increased rate of fracture healing, in favor of burosumab treated patients, was observed during the first 24 weeks of burosumab treatment and this increased up to 48 weeks of treatment. Placebo patients who crossed over to burosumab showed a similar increased rate of fracture healing. The safety profile was consistent with what has been previously observed in this study and in other open label studies of burosumab 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.

"This longer term data on symptom improvement and fracture healing support burosumab's potential value in treating serious disease symptoms and promoting bone healing in adult patients with XLH," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "The continued clinical improvements in patients and the new data demonstrating a significant decrease in pain medication use after treatment with burosumab provide further support for the potential value in the treatment of adults with XLH."

"This study provides valuable additional long term data for 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."

"The longer term data from this adult Phase 3 study demonstrates the potential of burosumab to positively impact the lives of patients with XLH and we look forward to progressing our discussions with the regulatory bodies in Europe and the US," said Dr. Tom Stratford, President and CEO of Kyowa Kirin International.

48-Week 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 a 24-week double blind period. After 24 weeks, patients from both treatment arms continued on to an open-label period, during which they all received 1mg/kg of burosumab every four weeks.

From 24 to 48 weeks of treatment, 84% of patients who had received burosumab since the beginning of the study (n=68) achieved and maintained serum phosphorus levels above the lower limit of normal (2.5 mg/dL). 89% of patients who crossed over from placebo to burosumab after 24 weeks (n=66) achieved and maintained serum phosphorus levels above the lower limit of normal.

Patients treated with burosumab showed continued improvement in stiffness and physical function as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®). For patients treated with burosumab, stiffness further improved from a mean change of 7.42 points at 24 weeks to 16.03 points at 48 weeks. Patients who crossed over from placebo to burosumab treatment had a mean change of 15.82 points from 24 to 48 weeks. Physical function also further improved from a mean change of 2.78 points at 24 weeks to 7.76 points at 48 weeks. For patients in the crossover group, physical function improved by a mean change of 8.18 points from 24 to 48 weeks.

Burosumab was associated with a reduction in pain measured by the Brief Pain Inventory Question 3 (BPI Q3; pain at its

worst in the last 24 hours), as well as a reduction in the use of pain medication. For patients treated with burosumab, pain scores further improved from a mean change of 0.81 points at 24 weeks to 1.09 points at 48 weeks. Patients who crossed over from placebo to burosumab treatment had a mean change of 1.18 points from 24 to 48 weeks. The patient frequency of reported opioid use decreased by 76% from 17 patients (25%) at baseline to four patients (6%) at week 48 in the burosumab group, and by 70% from 13 patients (20%) to four patients (6%) in the crossover group. The patient frequency of reported nonsteroidal anti-inflammatory drugs (NSAIDs) use decreased by 72% from 47 patients (69%) at baseline to 13 patients (19%) at week 48 in the burosumab group, and by 74% from 43 patients (65%) to 11 patients (17%) in the crossover group.

Burosumab treatment resulted in increased healing of fractures (active fractures and pseudofractures) compared to placebo at week 24, and this improvement continued through 48 weeks. When evaluating follow-up X-rays in the 52% of patients with identified fractures or pseudofractures at baseline, the 43% rate of fracture healing observed at 24 weeks on burosumab increased to 63% at 48 weeks. In the crossover group which had an 8% rate of fracture healing at 24 weeks, the rate increased to 35% at week 48. The crossover patient group fracture healing result was consistent with the effect observed in the first 24 weeks of the burosumab group treatment.

Safety Results

There was no difference in the overall frequency of treatment emergent serious and non-serious adverse events, treatment related adverse events and serious adverse events between the group who received burosumab for the 48-week period compared to the group who received placebo for the 24-week double-blind period and then crossed over to burosumab. The safety profile at 48 weeks was generally similar to that observed at 24 weeks. The most common adverse events in patients during treatment with burosumab ($\geq$10%) were arthralgia (24%), nasopharyngitis (22%), headache (20%), back pain (16%), tooth abscess (13%), fatigue (13%), restless leg syndrome (11%), pain in extremity (11%), pain (11%), toothache (11%), vitamin D deficiency (10%), and musculoskeletal pain (10%). Eleven % of patients who received burosumab experienced clinical symptoms compatible with hypersensitivity. There were 15 patients who experienced serious adverse events (SAEs) during treatment with burosumab, but none of these SAEs were considered treatment-related. No meaningful changes 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, as previously reported. During the open-label period, seven patients discontinued treatment. No discontinuations were related to adverse events or tolerability. There has been one non-treatment related death due to a car accident that was reported after the Week 48 data cutoff date.

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 South 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. Secondary and other endpoints include pain measured by BPI Q3, stiffness and physical function, both measured by WOMAC®, radiographic healing of active fractures/pseudofractures, and safety. After 24 weeks, all patients receive burosumab through the 72-week open-label extension period of the study.

Ultragenyx is conducting a second 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 IgG1 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 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.

About Ultragenyx

Ultragenyx is a 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 is a wholly owned subsidiary of Kyowa Hakko Kirin and is a rapidly growing specialty pharmaceutical company engaged in the development and commercialization of prescription medicines for the treatment of unmet therapeutic needs in Europe and the United States. Kyowa Kirin International 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 relating to Ultragenyx's expectations regarding plans for its clinical programs and clinical 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, such as the regulatory approval process, the timing of 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 Ultragenyx in general, see Ultragenyx's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 3, 2017, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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