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Ultragenyx and Kyowa Hakko Kirin Announce Additional Burosumab Data in X-Linked Hypophosphatemia (XLH) and Tumor-Induced Osteomalacia (TIO) at ASBMR

Positive data in bone disease in pediatric XLH patients under 5 years old and in TIO patients

NOVATO, Calif. and TOKYO, Sept. 11, 2017 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), a biopharmaceutical company focused on the development of novel products for rare and ultra-rare diseases, and Kyowa Hakko Kirin Co., Ltd. (Kyowa Hakko Kirin) today announced positive data from two ongoing Phase 2 studies - 40 week data from the study in children less than five years old with X-linked hypophosphatemia (XLH) and 24 week data from the study in adult tumor-induced osteomalacia (TIO) patients. Data presented at the American Society for Bone and Mineral Research (ASBMR) 2017 Annual Meeting also included a late-breaker presentation of 24-week data from the Phase 3 study in adult XLH patients, a presentation of 64-week data from another Phase 2 study in pediatric XLH patients (5 to 12 years old), and a poster on functional outcomes in the patients enrolled in this pediatric Phase 2 study. Ultragenyx is conducting the studies under a collaboration and license agreement with Kyowa Hakko Kirin to develop and commercialize burosumab.

"The results from the under five year old study support the value of early treatment initiation with burosumab in XLH patients in treating bone disease," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "The early improvements in bowing observed in these younger patients is a particularly important result for the treatment of XLH bone disease."

"These data are a product of our efforts to develop this antibody in order to make a positive contribution to the lives of patients with XLH and TIO worldwide," said Mitsuo Satoh, Ph.D., Executive Officer, Vice President, Head of R&D Division of Kyowa Hakko Kirin. "We will continue to conduct studies that strengthen the clinical evidence base for burosumab to contribute to patients with XLH and TIO worldwide."

Phase 2 Under 5 Study in XLH

The open-label Phase 2 study enrolled 13 children between the ages of one and four years old (mean age 2.9 years), 12 of whom had previously been on oral phosphate/active vitamin D therapy. This 64-week study is assessing the safety, pharmacodynamics, and efficacy of burosumab administered subcutaneously every 2 weeks. All patients received 0.8mg/kg starting dose and have completed 40 weeks of treatment.

Burosumab increased mean serum phosphorus levels by 1.2 mg/dL into the low normal range after one week of treatment and these levels were maintained through week 40 with 77% of children achieving normal serum phosphorus levels at week 40. Serum 1,25 dihydroxy vitamin D levels were also increased from baseline to week 40 of treatment.

All patients had rickets at baseline and 12/13 patients had $RSS \geq 1.5$. Rickets severity was assessed at 40 weeks using the RSS scoring system. The mean total RSS score improved significantly (59% reduction) at week 40 ($p < 0.0001$). The change in rickets severity was also assessed at week 40 by the RGI-C score which showed substantial healing (RGI-C score > 2) in all patients ($p < 0.0001$). Burosumab treatment also resulted in significantly improved bowing as determined by RGI-C lower limb deformity ($p < 0.0001$). Additionally, mean levels of alkaline phosphatase were significantly reduced (-39%, $p < 0.0001$) in these patients at week 40.

All patients experienced one or more adverse events. There was one serious adverse event of a tooth abscess that was considered unrelated to burosumab treatment. All other events were assessed as mild or moderate in severity except for a Grade 3 food allergy that was considered unrelated to burosumab treatment. Three patients had injection site reactions and four patients experienced hypersensitivity events that were all mild and considered unrelated to burosumab treatment. No clinically meaningful changes were observed in mean serum calcium, urinary calcium and in serum intact parathyroid hormone. There have been no events of hyperphosphatemia and there have been no deaths or discontinuations from the study.

Phase 2 TIO Study

The open label dose-finding Phase 2 study is evaluating the safety and efficacy of burosumab in 17 adult patients with TIO. The co-primary endpoints in this 48 week study are change in serum phosphorus and key biopsy parameters of osteomalacia. In 16 patients with baseline and week 24 data, mean serum phosphorus, renal phosphate reabsorption (TmP/GFR) and serum 1,25 dihydroxy vitamin D levels increased after the first dose and over 24 weeks of treatment. The baseline mean serum phosphorus level of 1.6 mg/dL was well below the lower limit of normal of 2.5 mg/dL. The mean serum phosphorus level entered the normal range within two weeks of treatment, and was maintained in the low normal range through week 24 of treatment. At week 24 there was a statistically significant increase in mean percent change from baseline levels (51% and 38% respectively) of the bone turnover markers, Procollagen type 1 N-terminal propeptide (P1NP) and collagen type 1 cross-linked C-telopeptide of type I collagen (CTX).

All patients had moderate to severe osteomalacia at baseline as assessed by histomorphometric indices of osteomalacia. Four patients who completed 48 weeks of treatment had bone biopsy data. In three of these patients burosumab treatment was associated with improvements in histomorphometric indices of osteomalacia. One patient did not receive burosumab consistently. Burosumab demonstrated a clinically meaningful improvement in patient reported outcomes. At 24 weeks, patients experienced a statistically significant reduction in all four fatigue parameters as assessed by the Brief Fatigue Inventory (BFI). Burosumab also demonstrated a statistically significant increase in lower limb strength as seen with the increase in repetitions at 24 weeks in the Sit-to-Stand test ($p < 0.01$). These results are particularly relevant to the TIO population since weakness and fatigue are key clinical problems that these patients experience.

Adverse events occurred in all patients ($n=16$). Treatment-related adverse events were observed in seven patients (44%), and included, as previously disclosed, Vitamin D deficiency and rash, and dysgeusia, all mild in grade. Most adverse events were grade 1 or 2 and included two patients with injection site reactions and two patients with restless leg syndrome that were previously disclosed. Three patients had a serious adverse event (previously disclosed tumor progression, thoracic epidural tumor compression, and a mesenchymal tumor progression). None of the serious adverse events were considered treatment related and all of these patients had a history of tumor progression at baseline and one patient discontinued to treat their tumor progression. No clinically meaningful changes were observed in mean serum calcium, urinary calcium and in serum intact parathyroid hormone.

About Burosumab

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 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.

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. 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 regarding treatment implications for patients, 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 Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on July 28, 2017, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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