Ultragenyx and Kyowa Kirin Announce Positive 64-Week Results for Crysvita® (burosumab) from Phase 3 Study in Children with X-linked Hypophosphatemia (XLH)

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Results Confirm and Extend 40-Week Findings that Treatment with Crysvita is Superior to Conventional Therapy

NOVATO, Calif., TOKYO and LONDON, Feb. 14, 2019 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), a biopharmaceutical company focused on the development of novel products for serious rare and ultra-rare genetic diseases, Kyowa Hakko Kirin Co. Ltd (Kyowa Hakko Kirin), and Kyowa Kirin International PLC (Kyowa Kirin International) today announced positive results of a 64-week efficacy and safety analysis of the randomized active-controlled Phase 3 study of Crysvita® (burosumab) in children with X-linked hypophosphatemia (XLH) compared with oral phosphate and active vitamin D (current conventional therapy).

The new results showed that Crysvita was superior to conventional therapy for all key efficacy endpoints, showing a meaningful improvement in rickets severity, lower limb deformity, growth, and physical functioning as demonstrated by increases in distance walked. The 64-week safety profile was similar to that observed at 40 weeks and in other Crysvita pediatric XLH studies.

The companies announced in May 2018 that the Phase 3 trial had met its primary endpoint, demonstrating that Crysvita was superior to conventional therapy in improving rickets after 40 weeks of treatment ($p<0.0001$). Crysvita is an antibody that blocks fibroblast growth factor 23 (FGF23), a hormone that causes an excess of phosphate urinary excretion and suppresses active vitamin D production by the kidney.

“We are very encouraged that these 64-week efficacy and safety results continue to demonstrate that Crysvita is significantly more effective than conventional therapy in normalizing phosphorus levels, reducing rickets, reducing lower leg deformity and improving growth in children with XLH. These new data demonstrate that Crysvita is disease-modifying and that oral phosphate and active vitamin D are not a sufficient treatment option for these children,” said Camille L. Bedrosian, M.D., Chief Medical Officer of Ultragenyx. “Importantly, these longer-term data show that children with XLH may be able to experience more normal growth when treated with Crysvita. Based on these compelling data, we plan to submit a supplemental Biologics License Application to the U.S. FDA for Crysvita in XLH in 2019.”

“These are excellent results which further expand our understanding of Crysvita’s value to pediatric patients with XLH,” said Mitsuo Satoh, Executive Officer, Vice President Head of Research and Development Division of Kyowa Hakko Kirin. “We are now focusing our efforts on working with health authorities to make Crysvita available for XLH patients in more countries and regions.”

Phase 3 Pediatric XLH Study Design

The randomized, active-controlled, open-label Phase 3 clinical study enrolled 61 patients ages 1 through 12 in the U.S., Europe, Canada, Australia, Japan and Korea, and compared the efficacy and safety of Crysvita (n=29) to conventional therapy (n=32). The study’s primary endpoint was the change in rickets at 40 weeks, assessed by three independent blinded pediatric radiologists using the radiographic global impression of change (RGI-C) scale. Secondary endpoints included additional rickets assessments using the RGI-C scale and the Thacher Rickets Severity Scoring (RSS) system, pharmacodynamic assessments, changes in growth velocity and height, walking ability, patient-reported outcomes assessing pain, fatigue and physical function, and safety. All endpoints were also evaluated at 64 weeks, as were the RGI-C lower limb deformity and height z score. Prior to study enrollment, all patients received conventional therapy for an average of approximately four years. Patients in the Crysvita treatment group received a starting dose of 0.8 mg/kg administered subcutaneously every two weeks, with dose increases up to 1.2 mg/kg implemented in eight patients. Patients in the conventional therapy arm received the local standard regimen based on expert guidelines with ongoing optimization by each patient’s physician.

Results from the 64-week efficacy and safety analyses showed the following:

Bone Disease Results after 64 Weeks of Treatment with Crysvita, versus Conventional Therapy

- Rickets scores were superior with Crysvita compared to conventional therapy, as assessed by three independent blinded pediatric radiologists using the Rickets Global Impression of Change (RGI-C) Global Score (LS mean treatment difference of +1.02, $p<0.0001$).
- RGI-C scores showing substantial healing of rickets (RGI-C ≥+2.0) was observed in 86.2% of patients receiving Crysvita compared to 18.8% of patients receiving conventional therapy ($p=0.0002$).
- Rickets Severity Scores (RSS) improved more with Crysvita compared to conventional therapy (LS mean treatment difference of -1.21, $p<0.0001$).

- Mean serum alkaline phosphatase levels as a biochemical measure of rickets were decreased by Crysvita into the normal range and were superior to conventional therapy at 64 weeks ($p<0.0001$).
- Lower limb deformity (RGI-C score for bowing/limb deformity) was reduced more with Crysvita compared with conventional therapy (LS mean treatment difference +0.97, $p<0.0001$).
- Growth during Crysvita treatment demonstrated a statistically significant improvement as shown by a greater increase in standing height/recumbent length z-score compared with conventional therapy (LS mean treatment difference +0.14, $p=0.0490$).
- Walking ability as measured by the six-minute walk test (6MWT) improved with Crysvita treatment compared to conventional therapy (LS mean treatment difference +45.6 meters, $p=0.0399$).

Metabolic Results

- Mean serum phosphorus levels reached the lower limit of normal range with Crysvita, unlike the small increase associated with conventional therapy. At baseline, patients in both the Crysvita and conventional therapy arms had mean serum phosphorus levels and mean renal phosphate reabsorption levels below the lower limits of normal. In the Crysvita arm, mean serum phosphorus and renal phosphate reabsorption levels post-baseline through Week 64 were in the normal range. In comparison, in the conventional therapy arm, mean serum phosphorus and renal phosphate reabsorption levels remained below the lower limits of normal through Week 64. The treatment differences between Crysvita and conventional therapy were significant ($p<0.0001$).
- Patients in both the Crysvita and conventional therapy arms demonstrated increases in serum 1,25-dihidroxy vitamin D and maintained levels within the normal range through 64 weeks.

Safety and Tolerability Results
The Crysvita safety profile observed at week 64 was generally consistent with data from Week 40 and is similar to other Crysvita pediatric XLH trials. At 64 weeks, there were no treatment discontinuations and no deaths reported in the study. There were three serious adverse events in the Crysvita arm and three serious adverse events in the conventional therapy arm, none of which were considered treatment-related. In the Crysvita arm, 51.7% of patients had injection site reactions; all but one were mild and none were considered serious. No clinically meaningful changes were observed in mean serum calcium and serum intact parathyroid hormone in either treatment arm, and there were no hyperphosphatemia events. No clinically significant changes were observed in renal ultrasounds pre-and post-treatment in either treatment arm.

About X-Linked Hypophosphatemia (XLH)
XLH is a rare, hereditary, progressive and lifelong skeletal disorder characterized by renal phosphate wasting caused by excess FGF23 production. It affects both children and adults. In children, XLH causes rickets that leads to lower-extremity deformity, delayed growth and decreased height. Adults with XLH have an increased risk of fractures.

About Crysvita
Crysvita is a 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. Phosphate wasting in XLH is caused by excessive levels and activity of FGF23. Crysvita is designed to bind to and thereby inhibit the biological activity of FGF23. By blocking excess FGF23 in patients, Crysvita is intended to increase phosphate reabsorption from the kidney and increase the production of vitamin D, which enhances intestinal absorption of phosphate and calcium.

Crysvita® (burosumab) is approved by the U.S. Food and Drug Administration (FDA) and by Health Canada for the treatment of XLH in adult and pediatric patients one year of age and older, and has received European conditional marketing authorization for the treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons. This Phase 3 pediatric study is serving as a confirmatory study in Europe; Ultragenyx also has submitted regulatory filings for Crysvita for XLH in, Brazil and Colombia.

Kyowa Hakko Kirin, Kyowa Kirin International, a wholly owned subsidiary of Kyowa Hakko Kirin, and Ultragenyx have been collaborating in the development and commercialization of Crysvita globally, based on the collaboration and license agreement between Kyowa Hakko Kirin and Ultragenyx.

INDICATION *(IN THE U.S.)*

Crysvita is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

IMPORTANT SAFETY INFORMATION

Crysvita should not be taken if:

- An oral phosphate supplement and a specific form of vitamin D supplement are taken
- Phosphorus levels from a blood sample are within or above the normal range for age
- Kidney problems are present

What is the most important information to know about Crysvita?

- Some patients developed allergic reactions (rash and hives) while taking Crysvita. Doctors will monitor for symptoms of an allergic reaction while Crysvita is taken.
- High levels of phosphorus in the blood have been reported in some patients taking Crysvita. This may be related to a risk of high calcium levels in the kidneys. Doctors will collect samples to monitor levels.

- Administration of Crysvita may result in reactions at the injection site, such as hives, reddening of the skin, rash, swelling, bruising, pain, severe itching of the skin, and collection of blood outside of a blood vessel (hematoma).

What are the possible side effects of Crysvita?

- The most common adverse reactions seen in children with XLH:
    - Headache
    - Injection site reaction
    - Vomiting
    - Fever
    - Pain in arms and legs
    - Decreased vitamin D levels
    - Rash
    - Toothache
    - Muscle pain
    - Tooth infection
    - Dizziness
- The most common adverse reactions seen in adults with XLH:
    - Back pain
    - Headache
    - Tooth infection
    - Restless leg syndrome
    - Decreased vitamin D levels
    - Dizziness
    - Constipation
    - Phosphorus levels increased in the blood
- Narrowing of the spaces within the spine is common in adults with XLH and pressure on the spinal cord has been reported in adults taking Crysvita. It is not known if taking Crysvita worsens the narrowing of the spaces within the spine or the pressure on the spinal cord.

Before taking Crysvita, doctors should be informed about all medical conditions, including if:

- Pregnant, thinks one may be pregnant, or plan to become pregnant. There is not enough experience to know if Crysvita may harm an unborn baby. Report pregnancies to the Kyowa Kirin, Inc. Adverse Event reporting line at 1-888-756-8657.
- Breastfeeding or plan to breastfeed. There is not enough experience to know if Crysvita passes into breast milk. Women should talk with their doctors about the best way to feed their babies while taking Crysvita.

While taking Crysvita, doctors should be informed if one experiences:

- An allergic reaction such as rash or hives
- A rash, swelling, bruising or other reaction at the injection site
- New or worsening restless leg syndrome

These are not all the possible side effects of Crysvita. Doctors should be contacted for medical advice about side effects.

Side effects may be reported to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. Side effects may also be reported to Kyowa Kirin, Inc. at 1-888-756-8657.

Please see full Prescribing Information for additional Important Safety Information.

About Ultragenyx Pharmaceutical Inc.
Ultragenyx is a biopharmaceutical company committed to bringing to patients novel products for the treatment of serious rare and ultra-rare genetic diseases. The company has built a diverse portfolio of approved therapies and product candidates aimed at addressing diseases with high unmet medical need and clear biology for treatment, 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.

Ultragenyx Forward-Looking Statements
Except for the historical information contained herein, the matters set forth in this press release, including statements related to Ultragenyx's expectations regarding plans for its clinical programs, future regulatory interactions, and the sufficiency for, and timing of, regulatory submissions and approvals, 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 products and 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 6, 2018, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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