Ultragenyx and Kyowa Kirin Announce Publication of Phase 2 Study Results Demonstrating that Crysvita® (burosumab) Improved Outcomes in Children with X-linked Hypophosphatemia in the New England Journal of Medicine

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Pediatric Study Demonstrated Improvements in Rickets Severity, Growth, Pain and Physical Activity in Children with Debilitating, Lifelong Hereditary Disease

NOVATO, Calif., TOKYO, JAPAN, and LONDON, May 23, 2018 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), Kyowa Hakko Kirin Co. Ltd, and Kyowa Kirin International PLC today announced that the results of a pediatric Phase 2 clinical trial of Crysvita® (burosumab) for the treatment of X-linked hypophosphatemia (XLH) in children aged 5 to 12 years were published online by the *New England Journal of Medicine (NEJM).* The results demonstrated that Crysvita improved rickets severity, growth, pain and physical function, and increased serum phosphorus and renal phosphate reabsorption. Adverse events were consistent with those previously observed for Crysvita for the treatment of XLH in children. Topline results from this study were previously announced in April 2017.

XLH is a rare, chronic progressive musculoskeletal disorder that affects children and adults. Crysvita is the first treatment to target the underlying pathophysiology of XLH – excess production of fibroblast growth factor 23 (FGF23), a hormone that regulates phosphate excretion and active vitamin D production by the kidney. In the *NEJM* article entitled "Burosumab Therapy in Children with X-Linked Hypophosphatemia" the authors state, "Inhibition of FGF-23 activity with burosumab, a recombinant human lgG1 monoclonal antibody, was associated with an increase in renal tubular phosphate reabsorption and the correction of hypophosphatemia in children with X-linked hypophosphatemia. The improvement in phosphate metabolism corresponded to a decrease in the severity of rickets. The healing of rickets probably contributed to concurrent improvements in growth and physical activity and a reduction in pain."

"This study was the natural extension of recent discoveries related to disease mechanisms in XLH, and in particular FGF23's role as a mediator of renal phosphate metabolism," said Tom Carpenter, M.D., the lead study investigator, Director of the Yale Center for X-Linked Hypophosphatemia, and Professor of Pediatric Endocrinology at Yale University School of Medicine. "The therapeutic approach taken, to directly inhibit FGF23's renal actions, demonstrates the potential advantages to therapy of metabolic disease when targeting a central disease mechanism. Sustained improvements in serum phosphorus resulted, with corresponding improvement in skeletal abnormalities. The approach should prove to be an important advance in the therapy of XLH."

On April 17, 2018, the U.S. Food and Drug Administration (FDA) approved Crysvita for the treatment of XLH in adult and pediatric patients 1 year of age and older. On February 23, 2018, Crysvita received a positive European Commission decision granting conditional marketing authorization to Crysvita for the treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons. Data from this Phase 2 study were included in both the U.S. and European regulatory applications.

"XLH causes a significant burden on children and their families and the consequences of the disease can affect patients for their entire lives," said Camille L. Bedrosian, M.D. Chief Medical Officer of Ultragenyx. "In this Phase 2 study, Crysvita showed a clear effect in improving bone health and growth in children with XLH, the most common inherited form of rickets."

"I am delighted that these results have been accepted by the *New England Journal of Medicine*, a world-leading medical journal with a mission to publish "ground breaking" research," said Mitsuo Satoh, Ph.D., Executive Officer, Vice President Head of R&D Division of Kyowa Hakko Kirin. "We will continue our R&D activities that strengthens the clinical evidence base for burosumab to contribute to patients all over the world."

Phase 2 Study Design

The randomized, multicenter, open-label, dose-finding Phase 2 study enrolled 52 children aged 5 to 12 years with XLH at nine sites in the United States and EU. Patients were randomized to receive Crysvita subcutaneously either every two or four weeks for 64 weeks. The primary endpoint was the change in rickets severity as measured by Rickets Severity Score and the Radiographic Global Impression of Change. Secondary endpoints included changes in: metabolic measures including serum phosphorus, 1,25 dihydroxy vitamin D, and serum alkaline phosphatase; growth; physical ability; patient-reported pain and functional disability; and safety.

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.

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 one 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 that were seen in children with XLH are:
    - 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 that were seen in adults with XLH are:
    - 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:

- One is pregnant, thinks she may be pregnant, or plans to become pregnant. There is not enough experience to know if Crysvita may harm an unborn baby. Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-888-756-8657.
- One is breastfeeding or plans 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 Ultragenyx at

1-888-756-8657.

Please see full Prescribing Information for additional Important Safety Information.

About Ultragenyx

Ultragenyx is a biopharmaceutical company committed to bringing to patients 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.

Ultragenyx Forward-Looking Statements

Except for the historical information contained herein, the matters set forth in this press release, including statements relating to the expected importance of a therapeutic approach as an advance in the therapy of XLH, 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 May 8, 2018, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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