Ultragenyx and Kyowa Kirin Announce Topline Phase 3 Study Results Demonstrating Superiority of Crysvita® (burosumab) Treatment to Oral Phosphate and Active Vitamin D in Children with X-Linked Hypophosphatemia (XLH)

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Substantial Healing of Rickets Observed in 72% of Patients Treated with Crysvita Compared to 6% of Patients Receiving Conventional Therapy at 40 Weeks

NOVATO, Calif. and TOKYO and LONDON, May 17, 2018 (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 that the Phase 3 study of Crysvita® (burosumab) met its primary endpoint demonstrating that Crysvita was superior to oral phosphate and active vitamin D (conventional therapy) in improving rickets in children with X-linked hypophosphatemia (XLH) after 40 weeks of treatment (LS Mean treatment difference of +1.14, $p<0.0001$). The study also showed improvement in important metabolic and functional measures with Crysvita treatment, and a safety profile similar to that observed in other Crysvita pediatric XLH studies. Crysvita is an antibody that blocks fibroblast growth factor 23 (FGF23), a hormone that causes phosphate urinary excretion and suppresses active vitamin D production by the kidney.

"This is the first study that directly compares Crysvita to conventional therapy for XLH, and we have now clearly demonstrated that Crysvita has a rapid and profound effect on the underlying disease, an outcome that was not achieved with conventional therapy," said Camille L. Bedrosian, M.D. Chief Medical Officer of Ultragenyx. "These data reinforce the results seen in our earlier Phase 2 studies, and we believe that Crysvita will transform the treatment of XLH in children."

"The results of this important controlled study demonstrate the value of directing therapy at the mechanism of renal phosphate wasting in XLH," said the lead study investigator, Erik Imel, M.D., Associate Professor of Medicine and Pediatrics at Indiana University School of Medicine. "While prior conventional therapy fails to improve renal phosphate wasting, Crysvita works to improve serum phosphorus by correcting the renal phosphate wasting. The differences in mechanism are clearly important to outcomes as demonstrated in this study. By comparing XLH patients treated with Crysvita to patients treated with conventional therapy, we are finally able to demonstrate the magnitude of benefit on parameters of serum phosphorus, bone metabolism, and improvements in the skeleton."

"I am pleased that the study provides valuable data for pediatric patients with XLH," said Mitsuo Satoh, Executive Officer, Vice President Head of Research and Development Division of Kyowa Hakko Kirin. "I believe Crysvita has the potential to be an effective treatment option for patients with XLH."

Phase 3 Pediatric XLH Study

The randomized, open-label Phase 3 clinical study enrolled 61 patients ages one 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. 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 five patients. Patients in the conventional therapy arm received the local standard regimen based on expert guidelines with ongoing optimization by each patient's physician.

Bone Disease Results

The study met its primary endpoint demonstrating that Crysvita significantly improved rickets compared to conventional therapy, as assessed by three independent blinded pediatric radiologists using the RGI-C scale. In addition, substantial healing (RGI-C ≥ +2.0) was observed in 72% of patients receiving Crysvita compared to 6% of patients receiving conventional therapy.

Rickets severity was also assessed using the RSS scoring system, which showed that patients treated with Crysvita showed a 2.8-fold improvement in rickets compared to patients receiving conventional therapy.

Endpoint	Treatment Effect		Treatment difference (95% CI)
	Crysvita n=29	Conventional therapy n=32	Crysvita vs. conventional therapy
RGI-C Score (Primary Endpoint)			
LS Mean*	+1.92	+0.77	1.14 (0.83, 1.45) P<0.0001
Substantial healing, % patients (RGI-C≥ +2.0)	72%	6%	Odds ratio: 39.139 (7.238, 211.656) P<0.0001
RSS Total Score			
LS Mean Change from Baseline	-2.04	-0.71	-1.34 (-1.74, -0.94) P<0.0001

**LS Mean: Least Squares Mean*

Metabolic Measures and Other Secondary Endpoints

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 40 were in the normal range. In the conventional therapy arm, mean serum phosphorus and renal phosphate reabsorption levels remained below the lower limits of normal over the 40-week period.

Endpoint	Treatment Effect		Treatment difference
	Crysvita n=29	Conventional therapy n=32	Crysvita vs. conventional therapy
Serum Phosphorus (mg/dL)*			
Mean baseline	2.42	2.30	
Mean post-baseline	3.38	2.55	
LS Mean Change from Baseline	1.00	0.23	0.77 p<0.0001

**Serum phosphorus lower limit of normal: 3.2mg/dL*

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 40 weeks.

Treatment with Crysvita showed a significant improvement in mean alkaline phosphatase levels into the normal range after 40 weeks of treatment, compared to conventional therapy. Patients treated with Crysvita also demonstrated a greater numeric but not statistically significant improvement in growth (height z-score and growth velocity) and in the six-minute walk test, compared to conventional therapy.

Safety and Tolerability

The Crysvita safety profile observed in this study was generally consistent with that seen in other Crysvita pediatric XLH studies. There were no treatment discontinuations and no deaths reported in the study. There were three serious adverse events in the Crysvita arm and one serious adverse event in the conventional therapy arm, none of which were considered treatment-related. In the Crysvita arm, 45% 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. No clinically significant changes were observed in renal ultrasounds pre-and post-treatment in either treatment arm.

Full results will be presented at an upcoming medical meeting.

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 active vitamin D, which enhances intestinal absorption of phosphate and calcium.

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 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. This Phase 3 pediatric study will serve as a confirmatory study in Europe; it was not required for the regulatory application in the U.S.

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 therapies 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 approved and investigational therapies 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 centred 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 realise 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 commercialisation 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 plans or expectations regarding the availability of Crysvita, and the potential effectiveness of Crysvita as a treatment option, 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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