

Ultragenyx and Kyowa Kirin Announce Submission of Supplemental Biologics License Application to U.S. FDA for Crysvita® (burosumab) for Tumor-Induced Osteomalacia (TIO)

Novato, Calif. and Tokyo, January 14, 2020 — Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), a biopharmaceutical company focused on the development of novel products for rare and ultra-rare diseases, and Kyowa Kirin Co., Ltd., (Kyowa Kirin, TYO: 4151) today announced that they submitted a supplemental Biologics License Application (sBLA) to the U.S. Food and Drug Administration (FDA) on December 18, 2019, for Crysvita® (burosumab) for the treatment of FGF23-related hypophosphatemia associated with phosphaturic mesenchymal tumors (tumor-induced osteomalacia; TIO) that cannot be curatively resected or localized. The companies expect to hear back from FDA on submission acceptance and review designation in February 2020.

“Approximately half of patients with TIO have tumors that cannot be surgically removed, leaving them with no other current treatment options,” said Camille L. Bedrosian, M.D., Chief Medical Officer of Ultragenyx. “We look forward to continuing to work closely with the FDA during the review process, with the goal of bringing Crysvita to patients with TIO in the U.S.”

The sBLA package includes data from two single-arm Phase 2 studies, a 144-week study in 14 adult patients conducted by Ultragenyx in the U.S. and an 88-week study in 13 adult patients conducted by Kyowa Kirin in Japan and South Korea. In both studies, Crysvita was associated with increases in serum phosphorus and serum 1,25-dihydroxyvitamin D levels. Increased phosphate levels led to improvements in osteomalacia, mobility and vitality. Bone scans also demonstrated an increase in healed fractures and a decrease in new fractures during Crysvita treatment. During the studies, adverse events generally reflected the patients’ underlying disease, and there were no serious treatment-related adverse events.

Crysvita is approved by the FDA for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients six months of age and older, and by Health Canada and Brazil’s National Health Surveillance Agency (ANVISA) for the treatment of XLH in adult and pediatric patients one year of age and older. It is approved by Japan’s Ministry of Health, Labor and Welfare (MHLW) for the treatment of FGF23-related hypophosphatemic rickets and osteomalacia. The medicine 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, and an application for the expanded use in adults with XLH is currently under review by the European Medicines Agency.

See below for Important Safety Information for Crysvita in X-linked hypophosphatemia.

About Tumor-Induced Osteomalacia (TIO)

TIO is caused by typically benign tumors that produce excess levels of fibroblast growth factor 23 (FGF23), causing phosphate wasting in the urine that leads to severe hypophosphatemia, osteomalacia, muscle weakness, fatigue, bone pain and fractures. The symptoms rapidly

resolve if the causal tumors or lesion can be resected; however, there are cases in which resection is not feasible or recurrence of the tumor occurs after resection. In patients for whom the tumor or lesion is inoperable, the current treatment consists of oral phosphate and/or vitamin D replacement. Efficacy of this management is often limited, as it does not treat the underlying disease and its benefits must be balanced with monitoring for potential risks such as nephrocalcinosis, hypercalciuria and hyperparathyroidism. An estimated 500-1,000 people in the United States have TIO, and approximately half of all cases are inoperable.

About Crysvisa

Crysvisa (burosumab-twza) is a recombinant fully human monoclonal IgG1 antibody, discovered by Kyowa Kirin, against the phosphaturic hormone 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 TIO and other hypophosphatemic conditions, including XLH, is caused by excessive levels and activity of FGF23. Crysvisa is designed to bind to and thereby inhibit the biological activity of FGF23. By blocking excess FGF23 in patients with TIO and XLH, Crysvisa 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 Kirin and Ultragenyx have been collaborating in the development and commercialization of Crysvisa globally based on the collaboration and license agreement between the parties.

INDICATION (IN THE U.S.)

Crysvisa is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.

IMPORTANT SAFETY INFORMATION

Crysvisa should not be taken if:

- An oral phosphate supplement and/or a specific form of vitamin D supplement are taken (such as calcitriol, paricalcitol, doxercalciferol, calcifediol).
- 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 Crysvisa?

- Some patients developed allergic reactions (rash and hives) while taking Crysvisa. Doctors will monitor for symptoms of an allergic reaction while Crysvisa is taken.

- High levels of phosphorus in the blood have been reported in some patients taking Crysvida. This may be related to a risk of high calcium levels in the kidneys. Doctors will collect samples to monitor levels.
- Administration of Crysvida 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 Crysvida?

- The most common adverse reactions that were seen in children with XLH are:
 - Fever
 - Injection site reaction
 - Cough
 - Vomiting
 - Pain in arms and legs
 - Headache
 - Tooth infection
 - Dental cavities
 - Diarrhea
 - Decreased vitamin D levels
 - Toothache
 - Constipation
 - Muscle pain
 - Rash
 - Dizziness
 - Nausea
- 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
 - Muscle spasms
 - 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 Crysvida. It is not known if taking Crysvida worsens the narrowing of the spaces within the spine or the pressure on the spinal cord.

Before taking Crysvida, doctors should be informed about all medications (including supplements) and medical conditions, including if:

- One is taking oral phosphate and/or active vitamin D (such as calcitriol, paricalcitol, doxercalciferol, calcifediol).
- One is pregnant, thinks she may be pregnant, or plans to become pregnant. There is not enough experience to know if Crysvida may harm an unborn baby. Report pregnancies to the Kyowa Kirin, Inc. Adverse Event reporting line at 1-888-756-8657.
- One is breastfeeding or plans to breastfeed. There is not enough experience to know if Crysvida passes into breast milk. Women should talk with their doctors about the best way to feed their babies while taking Crysvida.

While taking Crysvida, 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 Crysvida. 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 typically no approved therapies treating the underlying disease.

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 Kirin commits to innovate drug discovery driven by state-of-the-art technologies. The company focuses on creating new values in the four therapeutic areas: nephrology, oncology, immunology/allergy and neurology. Under the Kyowa Kirin brand, the employees from 36 group companies across North America, EMEA and Asia/Oceania unite to champion the interests of patients and their caregivers in discovering solutions wherever there are unmet medical needs. You can learn more about the business of Kyowa Kirin at www.kyowakirin.com.

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 and future regulatory interactions, 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, collaboration with third parties, including our collaboration with Kyowa Kirin, 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, 2019, and its subsequent periodic reports filed with the Securities and Exchange Commission.

###