



Ultragenyx and Kyowa Kirin Announce U.S. FDA Approval of Crysvida® (burosumab) for the Treatment of Tumor-Induced Osteomalacia (TIO)

- *First Approved Therapy in the United States for Patients with TIO Who Cannot Undergo Surgical Removal of Tumors*
- *TIO is Second FDA-Approved Indication for Crysvida, Which is Also Approved for the Treatment of X-linked Hypophosphatemia (XLH)*

NOVATO, Calif. and TOKYO, June 19, 2020 – Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), a biopharmaceutical company focused on the development and commercialization of novel products for rare and ultra-rare diseases, and Kyowa Kirin Co., Ltd. (Kyowa Kirin, TSE: 4151), a global specialty pharmaceutical company creating innovative medical solutions using the latest biotechnology, today announced that the U.S. Food and Drug Administration (FDA) has approved Crysvida® (burosumab) for the treatment of fibroblast growth factor 23 (FGF23)-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adults and pediatric patients 2 years of age and older. Crysvida is a human antibody that blocks excess activity of FGF23, a hormone that causes phosphate urinary excretion and suppresses active vitamin D production by the kidney.

“For approximately half of all individuals with TIO, surgical removal of the tumors is not possible, leaving these patients with no other treatment options. The FDA approval of Crysvida marks the first treatment option that addresses the cause of the severe hypophosphatemia and osteomalacia resulting from these rare tumors,” said Camille L. Bedrosian, M.D., Chief Medical Officer of Ultragenyx. “We plan to leverage our experience and existing infrastructure with Crysvida in X-linked hypophosphatemia to bring this important medicine to patients living with the rare, painful and debilitating disorder of TIO.”

“Since its approval, Crysvida has meant a great deal to patients and families that previously had no other treatment options. We are proud of the work that has been done to advance this discovery from our labs, through a robust clinical research program, and through the FDA’s priority review process, to make this treatment available to patients with TIO,” said Gary Zieziula, President, North America for Kyowa Kirin. “Our commitment to meeting the needs of patients with rare and serious diseases remains steadfast and we will continue to partner with the Ultragenyx team to address these needs with urgency.”

TIO is a rare disease caused by typically benign, slow-growing tumors that produce excess levels of FGF23, which is involved in phosphate reabsorption. Patients with TIO can experience symptoms including severe hypophosphatemia (low levels of phosphate in the blood), osteomalacia (softening of the bones), muscle weakness, fatigue, bone pain and fractures. There are an estimated 500 to 1,000 people in the United States with TIO, and approximately half of all cases are believed to be inoperable. In patients for whom the tumor or lesion is inoperable, the current treatment consists of oral phosphate and/or active vitamin D replacement. Efficacy of this management is often limited, and its benefits must be balanced with monitoring for potential risks.

This is the second FDA-approved indication for Crysvida, which was first approved in April 2018 for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients one year of age and older. The XLH indication was expanded in September 2019 to include infants as young as six months of age.

The FDA approval of Crysvida for TIO was based on data from two single-arm Phase 2 studies, a 144-week study in 14 adult patients conducted by Ultragenyx in the United States and an 88-week study in 13 adult patients conducted by Kyowa Kirin in Japan and South Korea. In both studies, Crysvida was associated with increases in serum phosphorus and serum 1,25-dihydroxyvitamin D levels. Increased phosphate levels led to improvements in osteomalacia. Additionally, whole body bone scans demonstrated reduced tracer uptake with long-term treatment suggesting healing of bone lesions. Most common adverse reactions (>10%) in TIO patients are: tooth abscess, muscle spasms, dizziness, constipation, injection site reaction, rash, and headache.

The FDA granted Priority Review designation for the supplemental BLA for TIO, which is reserved for drugs that treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.

To support access, Ultragenyx has a program called UltraCare™, which helps patients and caregivers understand insurance coverage and assists them in finding financial support for Ultragenyx medicines including Crysvida, and for the administration of them. Dedicated in-house UltraCare Guides are available Monday through Friday from 9 a.m. to 8 p.m. Eastern Time at 888-756-8657.

About Crysvida

Crysvida (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. Crysvida is designed to bind to and thereby inhibit the biological activity of FGF23. By blocking excess FGF23 in patients with TIO and XLH, Crysvida 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.

Crysvita is approved by the U.S. FDA for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients six months of age and older and FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adults and pediatric patients 2 years 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. In Japan, it is approved by the Ministry of Health, Labor and Welfare (MHLW) for the treatment of FGF23-related hypophosphatemic rickets and osteomalacia. In Europe, Crysvita 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.

Kyowa Kirin and Ultragenyx have been collaborating in the development and commercialization of Crysvita globally based on the collaboration and license agreement between the parties.

INDICATION (IN THE U.S.)

CRYSVITA® (burosumab-twza) is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for:

- The treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older.
- The treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- With oral phosphate and/or active vitamin D analogs (e.g., calcitriol, paricalcitol, doxercalciferol, calcifediol).
- When serum phosphorus is within or above the normal range for age.
- In patients with severe renal impairment or end stage renal disease.

WARNINGS AND PRECAUTIONS

Hypersensitivity

- Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment.

Hyperphosphatemia and Risk of Nephrocalcinosis

- For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels.

Injection Site Reactions

- Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment.

ADVERSE REACTIONS

Pediatric XLH Patients

- Adverse reactions reported in 10% or more of CRYSVITA-treated pediatric XLH patients across all studies are: pyrexia, injection site reaction, cough, vomiting, pain in extremity, headache, tooth abscess, dental caries, diarrhea, vitamin D decreased, toothache, constipation, myalgia, rash, dizziness, and nausea.

Adult XLH Patients

- Adverse reactions reported in more than 5% of CRYSVITA-treated adult XLH patients and in at least 2 patients more than placebo in one study are: back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, muscle spasms, and blood phosphorus increased.
- Spinal stenosis is prevalent in adults with XLH, and spinal cord compression has been reported. It is unknown if CRYSVITA therapy exacerbates spinal stenosis or spinal cord compression.

Adult TIO Patients

- Adverse reactions reported in 10% or more of CRYSVITA-treated adult TIO patients in two studies are: tooth abscess, muscle spasms, dizziness, constipation, injection site reaction, rash, and headache.

USE IN SPECIFIC POPULATIONS

- There are no available data on CRYSVITA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Serum phosphorus levels should be monitored throughout pregnancy. Report pregnancies to the Kyowa Kirin, Inc. Adverse Event reporting line at 1-888-756-8657.
- There is no information regarding the presence of CRYSVITA in human milk or the effects of CRYSVITA on milk production or the breastfed infant.

PATIENT COUNSELING INFORMATION

- Advise patients not to use any oral phosphate and/or active vitamin D analog products.
- Instruct patients to contact their physician if hypersensitivity reactions, injection site reactions, and restless leg syndrome induction or worsening of symptoms occur.

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 a complete discussion of the risks associated with CRYSVITA.

About Ultragenyx

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 innovative 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 40 group companies across North America, EMEA and Asia/Oceania unite to champion the interests of patients and their caregivers in discovering solutions to address 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 and projections regarding its future operating results and financial performance, anticipated cost or expense reductions, the timing, progress and plans for its clinical programs and clinical studies, future regulatory interactions, and the components and timing of regulatory submissions 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, 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, Ultragenyx's reliance on its third party partner, Kyowa Kirin Co., Ltd., for the supply of Crysvida, the effects from the COVID-19 pandemic on the company's business and operating results, smaller than anticipated market opportunities for the company's products and product candidates, the company's evolving commercial infrastructure, uncertainties related to insurance coverage and

reimbursement approval for the company's products, manufacturing risks, the uncertainties inherent in the clinical drug development process, including the potential for substantial delays and the risk that earlier study results may not be predictive of future study results, the lack of predictability in the regulatory approval process, the timing of regulatory filings and approvals (including whether such approvals can be obtained), and other matters that could affect sufficiency of existing cash, cash equivalents and short-term investments to fund operations, the company's future operating results and financial performance and the availability or commercial potential of Ultragenyx's 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 May 7, 2020, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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