



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

Novato, CA and Tokyo, Japan — September 10, 2019 — 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 plans to submit a supplemental Biologics License Application (sBLA) to the U.S. Food and Drug Administration (FDA) 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 decision to submit follows the completion of a pre-sBLA meeting with the FDA and agreement on the filing package. The submission of the Crysvita sBLA is planned for the first half of 2020 and will be based on the current clinical data package.

“Based on productive discussions with the FDA, we will be moving forward expeditiously with an sBLA filing for Crysvita in tumor-induced osteomalacia,” said Camille L. Bedrosian, M.D., Chief Medical Officer of Ultragenyx. “We look forward to working with the agency during the review process, and we are committed to getting this therapy to patients with this serious disease with significant unmet medical need.”

The BLA package will include data from two single-arm Phase 2 studies, a 144-week Phase 2 study in 14 adult patients conducted by Ultragenyx in the U.S. and an 88-week Phase 2 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 decrease in new fractures during Crysvita treatment. Adverse events generally reflected the patients’ underlying disease, and there were no serious treatment-related adverse events during the studies.

Crysvita is approved by the U.S. FDA, Health Canada, and Brazil’s National Health Surveillance Agency (ANVISA) for the treatment of X-linked hypophosphatemia (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.

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. There are an estimated 500-1,000 patients with TIO in the United States, and approximately half of all cases are inoperable.

About Crysvida

Crysvida (burosumab-twza) is a recombinant fully human monoclonal IgG1 antibody, discovered by Kyowa Hakko 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 vitamin D, which enhances intestinal absorption of phosphate and calcium.

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

Important Safety Information In X-Linked Hypophosphatemia

CONTRAINDICATIONS

- Do not use CRYSVITA with oral phosphate and active vitamin D analogs.
- Do not initiate CRYSVITA treatment if serum phosphorus is within or above the normal range for age.
- CRYSVITA is contraindicated in patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.

WARNINGS AND PRECAUTIONS

Hypersensitivity

- Hypersensitivity reactions (e.g. rash, urticaria) have been reported in patients with CRYSVITA. Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment.

Hyperphosphatemia and Risk of Nephrocalcinosis

- Increases in serum phosphorus to above the upper limit of normal may be associated with an increased 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

- Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment.

ADVERSE REACTIONS

Pediatric Patients

- The most common adverse reactions (more than 10%) in pediatric XLH patients are: headache, injection site reaction, vomiting, pyrexia, pain in extremity, vitamin D decreased, rash, toothache, myalgia, tooth abscess, and dizziness.

Adult Patients

- The most common adverse reactions (more than 5% and in at least 2 patients more than placebo) in adult XLH patients are: back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, 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.

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 Ultragenyx 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. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CRYSVITA and any potential adverse effects on the breastfed infant from CRYSVITA or from the underlying maternal condition.

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 August 2, 2019, and its subsequent periodic reports filed with the Securities and Exchange Commission.