KYOWA KIRIN

News release

Kyowa Kirin Announces Approval of Crysvita® (burosumab) for the Treatment of FGF23-related Hypophosphatemic Rickets and Osteomalacia in Japan

Tokyo, Japan, September 20th, 2019 – Kyowa Kirin Co., Ltd., (TYO: 4151, President and CEO: Masashi Miyamoto, "Kyowa Kirin") today announced that Crysvita® (burosumab) has been approved by Japan's Ministry of Health, Labor and Welfare (MHLW) for the treatment of FGF23-related hypophosphatemic rickets and osteomalacia.

Crysvita® is a recombinant fully human monoclonal IgG1 antibody, discovered by Kyowa Kirin, and is the first drug that directly targets fibroblast growth factor 23 (FGF23), a “phosphaturic” hormone. FGF23 reduces serum levels of phosphorus by regulating phosphate excretion and vitamin D activation in the kidney. Crysvita® has been developed to treat FGF23-related hypophosphatemic diseases, such as X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO).

By blocking excess activities of FGF23 in patients, Crysvita® restores phosphate reabsorption by the kidney, and increases the activation of vitamin D, which enhances intestinal absorption of phosphate. Thus, hypophosphatemia as well as bone mineralization defects can be ameliorated.

“I am pleased to hear such great news,” said Tomohiro Sudo, Head of Global Product Management Office of Kyowa Kirin, “Now, Crysvita has received approval in Japan, alongside the US FDA approval and pediatric approval by EMA in Europe, I hope this product will help more patients with FGF23-related hypophosphatemic rickets and osteomalacia.”

Crysvita® received orphan drug designation by the MHLW in Japan for FGF23-related hypophosphatemic rickets and osteomalacia.

Kyowa Kirin and Ultragenyx Pharmaceutical Inc. (Ultragenyx) have been collaborating in the

development and commercialization of burosumab globally based on a collaboration and license agreement between the two companies.

The Kyowa Kirin Group companies strive to contribute to the health and well-being of people around the world by creating new value through the pursuit of advances in life sciences and technologies.

About FGF23-related Hypophosphatemic Rickets and Osteomalacia

FGF23-related hypophosphatemic rickets and osteomalacia is an inclusive term of diseases caused by excessive actions of FGF23, which leads to impaired phosphate reabsorption in the renal proximal tubules. In Japan, the disease corresponds to vitamin D resistant rickets and osteomalacia (Intractable Diseases) and primary hypophosphataemic rickets and vitamin D resistant osteomalacia (Specific Pediatric Chronic Diseases). The term also encompasses diseases, such as X-linked hypophosphatemia (XLH), tumor-induced osteomalacia (TIO) and epidermal nevus syndrome (ENS). These diseases are rare, and skeletal disorders characterized by renal phosphate wasting.

The excess production of FGF23 in XLH patients is caused by inactivating mutations in the *PHEX* (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) gene while ADHR (autosomal dominant hypophosphatemic rickets) patients is reported to be reasoned at FGF23 gene mutation. Other relevant diseases of FGF23-related hypophosphatemic rickets and osteomalacia are TIO, in which excess FGF23 production is caused by tumors and ENS, in which it is caused by skin lesions.

About Crysvita® (burosumab)

Crysvita® (burosumab) is a recombinant fully human monoclonal IgG1 antibody, discovered by Kyowa Kirin Co., Ltd. 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 FGF23-related hypophosphatemic rickets and osteomalacia 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.

In 2018, the European Medicines Agency (EMA) granted a conditional marketing approval for Crysvita® for the treatment of XLH in children with radiographic evidence of bone disease from one year of age and older and in adolescents with growing skeletons. In the same year, Crysvita®

received approval from the US Food and Drug Administration (FDA) and Health Canada for pediatric and adult use.

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 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 https://www.kyowakirin.com

About Ultragenyx Pharmaceutical Inc.

Ultragenyx (NASDAQ: RARE) 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 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.

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