News release

Kyowa Kirin Announces European Commission (EC) Approval of CRYSVITA® (burosumab) for the Treatment of X-Linked Hypophosphataemia (XLH) in Older Adolescents and Adults

More people in Europe are now eligible for treatment with CRYSVITA, the only therapy that targets the underlying pathophysiology of XLH, a rare, life-long genetic disease that causes abnormalities in the bones, muscles and joints[1,2,3]

TOKYO, Japan, October 5, 2020 – Kyowa Kirin Co., Ltd. (TSE: 4151, Kyowa Kirin) today announced that the European Commission (EC) has approved CRYSVITA® (burosumab) for use in older adolescents and adults with the rare disease X-linked hypophosphataemia (XLH). CRYSVITA was previously approved for the treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons. With this expanded approval, all adolescents with radiographic evidence of bone disease, regardless of growth status, as well as adults with XLH are now also eligible for treatment with CRYSVITA.[4]

XLH is a life-long and progressive disease that typically presents in early childhood, causing lower limb deformities, stunted growth, and bone and joint pain.[5] Symptoms such as dental abscesses, osteoarthritis, enthesopathy (issues with the tendons), and hearing loss may also develop during adulthood.[6,7,8] As a result of the disease, some adults may require special equipment to improve their mobility.[9,10] The physical limitations as well as pain and stiffness caused by XLH can affect people's ability to work and socialise, their emotional wellbeing, and their capacity for self-care.[9]

"Until now, adults living with XLH have had limited treatment options for this progressive, disabling condition," said Dr Karine Briot, Hôpital Cochin, Paris, France. "Today's approval is an important advance as it means that for the first time these adult XLH patients have a treatment option developed to target the underlying processes that cause this challenging disease."

"Today's decision from the European Commission is a significant milestone for the management of XLH, a progressive and life-long disease that profoundly impacts the lives of both children and adults," said Abdul Mullick, President of Kyowa Kirin International. "As part of our commitment to life, we strive to answer the unmet medical needs of patients, their families, and the medical professionals who care for them. With this approval, older adolescents and adults with XLH will also be able to benefit from treatment with CRYSVITA, the only therapy that targets the underlying pathophysiology of this disease. We now will focus on ensuring access for as many people as possible in this expanded group of eligible patients."

The application to expand the marketing authorisation was based on data from two Phase 3 studies: the Phase 3 UX023-CL303 study, a randomised, double-blind, placebo-controlled trial investigating the safety and efficacy of burosumab in adults with XLH, and the Phase 3 UX023-CL304 study, an open-label, single-arm study investigating the effects of burosumab on osteomalacia (softening of the bones) in adults with XLH. These two studies found that burosumab increased and maintained serum phosphate levels in the normal range, helped to heal pseudofractures and fractures related to osteomalacia, and improved osteomalacia. Other endpoints showed that patients had less pain and stiffness, and their physical functioning and mobility improved with time.[11,12,13] The safety profile of burosumab was consistent with that observed in other burosumab studies, with adverse events including injection site reactions, hyperphosphataemia and hypersensitivity. There were no treatment-related serious adverse events.[11,12]

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 X-linked hypophosphataemia

X-linked hypophosphataemia (XLH) is a rare, genetic disease that causes abnormalities in the bones, muscles, and joints.[1,2,3] XLH is not life-threatening, but its burden is life-long and progressive, and it may reduce a person's quality of life.[5]

People with XLH have a genetic defect on the X-chromosome, which causes an excessive loss of phosphate through the urine and poor absorption from the gut, resulting in chronically low levels of phosphate in the blood.[5,14] Phosphate is a key mineral needed for maintaining the body's energy levels, muscle function, and the formation of healthy bones and teeth.[15,16] While there is no cure for XLH, therapies aimed at helping to restore phosphate to normal levels within the body may help to improve the symptoms of the disease.[12]

XLH is the most common form of hereditary rickets.[17] It can sometimes appear in individuals with no family history of the disease, but is usually passed down from a parent who carries the defective gene.[18]

About CRYSVITA® (burosumab)

CRYSVITA (burosumab) was created by Kyowa Kirin and is a recombinant fully human monoclonal IgG1 antibody against the phosphaturic hormone fibroblast growth factor 23 (FGF23). FGF23 is a hormone that reduces serum levels of phosphate by regulating phosphate excretion and active vitamin D production by the kidney. Phosphate wasting and resulting hypophosphataemia in X-linked hypophosphataemia (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 vitamin D, which enhances intestinal absorption of phosphate and calcium.

In 2018, the European Commission granted a conditional marketing authorisation for CRYSVITA for the

treatment of XLH with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons.[4] In the same year, CRYSVITA received approval from the US Food and Drug Administration (FDA) and Health Canada for paediatric and adult use.[19,20]

In 2019, CRYSVITA received approval from Japan's Ministry of Health, Labour and Welfare for the treatment of FGF23-related hypophosphataemic rickets and osteomalacia.

In January 2020, Swissmedic approved CRYSVITA for the treatment of adults, adolescents and children (one year of age and older) with XLH.[21]

Kyowa Kirin and Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE: Ultragenyx) have been collaborating in the development and commercialisation of CRYSVITA globally, based on the collaboration and licence agreement between Kyowa Kirin and Ultragenyx.

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 wherever there are unmet medical needs.

You can learn more about the business of Kyowa Kirin at: https://www.kyowakirin.com/

Kyowa Kirin International

http://www.international.kyowa-kirin.com / www.kyowakirin.com

Galabank Business Park

Galashiels, TD1 1QH

United Kingdom

References

[1] Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;3:R13-30.

[2] Orphanet. X-linked hypophosphatemia. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=89936. Last updated: January 2012. Last accessed: September 2020.

[3] Haffner D, Emma F, Eastwood DM, et al. Consensus Statement. Evidence-based guideline. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphatemia. *Nat Rev Nephrol*. 2019;15;435-455.

[4] European Medicines Agency. CRYSVITA EPAR product information. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/crysvita-epar-product-information_en.pdf. Last updated: March 2020. Last accessed: September 2020.

[5] Skrinar A, Dvorak-Ewell M, Evins A, et al. The lifelong impact of X-linked hypophosphatemia: Results from a burden of disease survey. *J Endocr Soc*. 2019;3:1321-1334.

[6] Lee JY, Imel EA. The changing face of hypophosphatemic disorders in the FGF-23 era. *Pediatr Endocrinol Rev*. 2013;10:367-379.

[7] Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol*. 2016;174:325-333.

[8] Ruppe MD. X-Linked Hypophosphatemia. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): University of Washington, 1993-2018. Available at: https://www.ncbi.nlm.nih.gov/books/NBK83985/. Last accessed: September 2020.

[9] Lo SH, Lachmann R, Williams A, et al. Exploring the burden of X-linked hypophosphatemia: a European multi-country qualitative study. *Qual Life Res*. 2020;29:1883-1893.

[10] Theodore-Oklota C, Bonner N, Spencer H, et al. Qualitative research to explore the patient experience of X-linked hypophosphatemia and evaluate the suitability of the BPI-SF and WOMAC® as clinical trial end points. *Value Health*. 2018;21:973-983.

[11] Insogna KL, Briot K, Imel EA, et al. A randomized, double-blind, placebo-controlled, Phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res*. 2018;33:1383-1393.

[12] Insogna KL, Rauch F, Kamenický P, et al. Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a Phase 3, single-arm, international trial. *J Bone Miner Res*. 2019;34:2183-2191.

[13] Portale AA, Carpenter TO, Brandi ML, et al. Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: Results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calcif Tissue Int*. 2019;105:271-284.

[14] Beck-Nielsen SS, Mughal Z, Haffner D, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet J Rare Dis*. 2019;14:58.

[15] Pesta D, Tsirigotis DN, Befroy DE, et al. Hypophosphatemia promotes lower rates of muscle ATP synthesis. *The FAESB Journal.* 2016;39:3378-3387.

[16] Unnanuntana A, Rebolledo BJ, Khair MM, et al. Diseases affecting bone quality: beyond osteoporosis. *Clin Orthop Relat Res*. 2011;469:2194-2206.

[17] Carpenter TO, Imel EA, Holm IA, et al. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26:1381-8.

[18] National Center for Advancing Translational Sciences. X-linked hypophosphatemia. Available at: https://rarediseases.info.nih.gov/diseases/12943/x-linked-hypophosphatemia. Last updated: February 2018. Last accessed: September 2020.

[19] CRYSVITA Prescribing Information. Available at: https://www.ultragenyx.com/file.cfm/29/docs/Crysvita_Full_Prescribing_Information.pdf. Last updated: June 2020. Last accessed: September 2020.

[20] Health Canada. Regulatory Decision Summary – CRYSVITA. Available at: https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00463. Last updated: April 2020. Last accessed: September 2020.

[21] Swissmedic. Crysvita®, injektionslösung (burosumabum). Available at: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/new-medicines/vrysvita-injektionsloesung_burosumabum.html. Last updated: January 2020. Last accessed: September 2020.