News release

Kyowa Kirin Receives Positive CHMP Opinion for the Expanded Use of CRYSVITA® (burosumab) to Include Older Adolescents and Adults for the Treatment of X-Linked Hypophosphataemia (XLH)

XLH is a rare, life-long genetic disease that causes abnormalities in the bones, muscles and joints[1,2,3]

TOKYO, Japan, 24 July 2020 – Kyowa Kirin Co., Ltd. (TSE:4151, Kyowa Kirin) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has recommended the expanded approval of CRYSVITA® (burosumab) to include older adolescents and adults living with the rare disease X-linked hypophosphataemia (XLH). The European Commission has already 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] The CHMP recommends that this approval is expanded to include all adolescents with radiographic evidence of bone disease, regardless of growth status, as well as adults with XLH. The CHMP opinion will now be reviewed by the European Commission, with a final decision expected in September 2020.

The signs and symptoms of XLH begin in early childhood causing lower limb deformities, shortened stature and pain. These can lead to difficulties with walking and physical functioning, affecting quality of life. The skeletal deformities coupled with unresolved hypophosphataemia mean the disease continues to progress in adults causing pain and stiffness, and multiple musculoskeletal deficits that can affect patients as early as in the second or third decade of life.[5]

“Today’s positive CHMP opinion marks a crucial step forward for the XLH community,” said Abdul Mullick, President of Kyowa Kirin International. “There is currently no approved therapy in Europe for older adolescents and adults with XLH that targets the underlying cause of this debilitating, progressive and life-long disease. Should CRYSVITA be approved for expanded use, it will enable adolescents to continue to receive the benefits of treatment after their bones have stopped growing, and offer adults with XLH a treatment that has been shown to reduce pain and stiffness, improve physical functioning and mobility, and heal pseudofractures and fractures. This expansion of the indication to a wider population aligns perfectly with our vision as a company and our commitment to life that guides our actions every day.”

The positive opinion from the CHMP 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 trial investigating the effects of burosumab on osteomalacia in adults with XLH.

"Adult XLH patients' response to conventional therapy, which includes phosphate and activated vitamin D, is variable and the evidence-base for its efficacy is limited," said Dr Karine Briot, Hôpital Cochin, Paris, France. "Having access to an efficacious treatment consistently from childhood through adulthood will be highly valuable to patients and to the physicians administering their care. Today's recommendation is an important step forward for all people with XLH and those who care for and support them."

"This achievement forms part of our mission to respond to the requests and hopes of patients living with diseases for which there is currently no adequate treatment," said Yoshihiro Furuya, SVP, Global Product Lead for CRYSVITA, GPMO of Kyowa Kirin. "We share this milestone with patients, their families and clinical investigators across Europe whose perseverance and commitment have made this progress possible."

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.[5,6] Phosphate is a key mineral needed for maintaining the body's energy levels, muscle function and the formation of healthy bones and teeth.[7,8] 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.[9]

XLH is the most common form of hereditary rickets.[10] 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.[11]

About CRYSVITA® (burosumab)

CRYSVITA (burosumab) was discovered 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.[12,13]

In 2019, CRYSVITA received approval from Japan's Ministry of Health, Labor 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.[14]

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 license 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/

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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: July 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: July 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] 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.

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

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

[9] 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.

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

[11] 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: July 2020.

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

[13] Health Canada. Regulatory Decision Summary – CRYSVITA. Available at: https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00463. Last updated: December 2018. Last accessed: July 2020.

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