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HEALTH TECHNOLOGY BRIEFING
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Burosumab for x-linked hypophosphataemia in adults

NIHRIO ID	12419	**NICE ID**	9729
Developer/Company	Kyowa Kirin Ltd.	**UKPS ID**	654561

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Burosumab is in clinical development for the treatment of adults with X-linked hypophosphataemia (XLH), and is currently licenced in children. XLH is an inherited disorder characterized by low levels of phosphate in the blood. Phosphate levels are low because phosphate is abnormally processed in the kidneys due to high levels of a protein called FGF23, which causes a loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones (rickets). For the past 40 years, therapy has primarily consisted of multiple daily doses of oral phosphate with active vitamin D. Due to adverse effects of this conventional therapy, the general practice and guidance has been to stop treatment at the end of growth and only treat adult patients who are symptomatic with XLH, leaving a substantial proportion of adults with no treatment.

Burosumab, administered by subcutaneous injection, is a monoclonal antibody (a type of protein) designed to recognise and attach to the FGF23 protein. By attaching to the FGF23 protein, the medicine blocks its activity, allowing the kidneys to reabsorb phosphate into the bloodstream and restore normal levels of phosphate in the blood. In studies of adults with XLH, burosumab is associated with normalisation of serum phosphorus, restoration of bone quality and improvements in pain, stiffness, fatigue, as well as healing of fractures compared to placebo.

PROPOSED INDICATION

Adults with X-linked hypophosphataemia (XLH).[1]

TECHNOLOGY

DESCRIPTION

Burosumab (Crysvita, KNR23) is a human immunoglobulin 1 (IgG1) monoclonal antibody to fibroblast growth factor 23 (FGF23).[2] By binding to FGF23, burosumab inhibits FGF23 signalling, thereby increasing tubular phosphate reabsorption and decreasing renal phosphate excretion, as well as increasing serum levels of 1,25(OH)2D and increasing gastrointestinal absorption of phosphate. As a result, serum phosphate levels increase, and, ultimately, bone mineralisation is improved and the risk of done disease is decreased.[3]

Burosumab is in clinical development for the treatment of adults with XLH, and is currently licenced in children.[4] A number of studies have been conducted evaluating burosumab in adults with XLH, including a phase III trial (NCT02537431), in which burosumab at 1.0 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, was given by subcutaneous injection every 4 weeks for up to 48 weeks.[1]

INNOVATION AND/OR ADVANTAGES

XLH is caused by mutations to the PHEX gene that regulates FGF23 production, which results in excessive circulating levels of FGF23 that causes phosphate wasting and subsequent impaired bone and teeth mineralisation. Treatment of patients with XLH with burosumab blocks FGF23 to normalise phosphate homeostasis, to increase circulating serum phosphate, decrease alkaline phosphatase and consequently reduce and reverse clinical signs and symptoms.[2]

Current treatment involves oral phosphate supplementation, which should be given as frequently as possible, for example, 4–6 times per day in young patients with high alkaline phosphatase levels, to maintain stable blood levels. Less frequent dosing (2–3 times daily) might improve adherence in adolescents.[5] Burosumab could therefore be a favourable treatment option, as it can be administered once monthly[1], as opposed to frequent daily doses of oral phosphate, which could cause adherence issues.[5] In addition, the general practice and guidance has been to stop treatment at the end of growth, and only treat symptomatic adult patients with XLH, leaving a large proportion of adult patients untreated.[5]

In studies of adults with XLH (18-65 years old), burosumab is associated with normalisation of serum phosphorus and restoration of bone quality which drives improvements in pain, stiffness, fatigue, as well as healing of pseudo-fractures and fractures compared to placebo.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Burosumab is licensed in the UK for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.[4] Common side effects in children include dizziness; headache; myalgia; pain in extremity; rash; tooth abscess; toothache.[7]

In 2018, the US Food and Drug administration (FDA) approved burosumab for the treatment of XLH in adults and children over one year of age. The FDA also awarded burosumab

breakthrough therapy designation in April 2018[8] and orphan drug designation in December 2009, for the treatment of adults and children aged one year and older, with XLH.[9]

In 2018, the European Medicines Authority (EMA) also designated burosumab as an orphan drug (EMEA/H/C/004275).[10]

Burosumab is also in clinical development for the treatment of tumour-induced osteomalacia (TIO) and epidermal nervus syndrome (ENS).[11]

PATIENT GROUP

DISEASE BACKGROUND

XLH is an inherited disorder characterised by low levels of phosphate in the blood. Phosphate levels are low because phosphate is abnormally processed in the kidneys, which causes loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones (rickets).[12]

XLH is caused by mutations in the *PHEX* gene on the X-chromosome, and inheritance is X-linked dominant. *PHEX* is involved in regulating the amount of phosphate in the body. Mutations in the gene lead to increased concentrations of FGF23, which regulates the reabsorption of phosphate in the kidneys. Too much FGF2 reduces the amount of phosphate reabsorbed by the kidneys, leading to hypophosphataemia.[13] The disease affects both sexes equally.[14]

The inadequate supply of phosphate in XLH has lifelong consequences for multiple body systems. XLH typically manifests in early childhood as rickets, skeletal deformities, short stature, and dental abscesses.[13,15,16] Children commonly suffer delayed walking, unusual gait, muscle weakness, and bone pain, as well as emotional and social challenges. Skeletal deformities and short stature acquired in childhood are irreversible after completion of growth. [15]

Chronic hypophosphatemia persists into adulthood; adults often develop multiple morbidities, including pseudofractures (where a radiograph shows formation of new bone with thickening of periosteum at site of an injury to bone), fractures, enthesopathies (calcification of the tendons, ligaments and joint capsules), and early-onset osteoarthritis, stiffness, and loss of physical function.[15] Dental problems are also very common in adults and hearing problems begin to develop at this stage.[12]

As with the clinical sequelae of XLH, the burden of XLH continues to evolve throughout adult life. Most adults with XLH report suffering from joint or bone pain on a daily basis. The lower limb deformities, the clinical sequelae observed in adults, along with pain, stiffness and fatigue have immense impact on their mobility, physical functioning and their ability to perform daily activities and limiting their social/family/work life. There have been reports of adults suffering emotionally, with depression, anxiety, and fears for the future.[15]

Conventional therapy involves multiple daily doses of oral phosphate supplementation, however, due to the known risks of these supplements, the general practice and guidance has been to stop treatment at the end of growth, and only treat symptomatic adult patients with XLH[5], leaving a substantial proportion of adults with no treatment. Surgical intervention is also required in adulthood due to the presence of multiple, musculoskeletal, non-musculoskeletal sequelae of chronic hypophosphataemia, such as hip and knee replacements, spinal surgery, dental surgery and parathyroidectomies.[15,17]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016, it was estimated that the UK prevalence of XLH is approximately 17.0 and 15.7 per million in children and adults respectively. This same 2016 study estimated an eight year reduction in survival, when compared to controls, although the observed increase in mortality in XLH is not known.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In adulthood, due to the known risks with conventional therapy, the general practice and guidance has been to stop treatment at the end of growth, and only treat symptomatic adult patients with XLH. For those that do take conventional therapy, since oral phosphate is rapidly absorbed in the small intestine and excreted into the urine within hours, it needs to be administered multiple times per day, the levels returning to baseline levels within 1.5 hours. Oral phosphate is generally poorly tolerated causing gastrointestinal symptoms such as diarrhoea, nausea and abdominal pain. Persistent normalisation of the serum phosphate level is not an achievable therapeutic goal with conventional therapy as attempting to normalise serum phosphate may lead to overtreatment with oral phosphate and increases the risk for treatment-related complications, such as secondary hyperparathyroidism.[5,12,16]

Skeletal response varies widely in individuals such that orthopaedic procedures are usually indicated to correct deformity (both angular and torsional) at the end of growth. Adults with XLH more frequently have hip and knee replacements than the general population. In adults, these conditions are unlikely to improve with medical management alone, which should nonetheless always accompany surgical management. In patients undergoing orthopaedic surgery, therapy might need to be discontinued if long-term bed rest and/or non-weight-bearing mobilization is anticipated to avoid hypercalciuria and/or hypercalcaemia due to increased bone resorption.[5]

Physical therapy is offered to provide pain relief, to improve physical function and fitness and to reduce XLH-related disability. To date, no disease-specific recommendations exist for physical therapy in patients with XLH, and programmes are based on recommendations of physical therapies for individuals with knee or hip osteoarthritis.[5]

CURRENT TREATMENT OPTIONS

Current treatment options for adults with XLH include:[5]

- Calcitriol or alfacacidol
- Oral phosphate supplementation

Burosumab is licensed in the UK for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.[4]

PLACE OF TECHNOLOGY

If licensed, burosumab will offer a treatment option for children over one year old, and adults with XLH, who currently have limited therapeutic options.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	NCT02537431, An Open-Label, Single-Arm, Phase 3 Study to Evaluate the Effects of KRN23 on Osteomalacia in Adults With X-linked Hypophosphatemia (XLH) **Phase III - completed** **Locations:** Europe (excluding the UK), USA and other countries **Study completion date:** December 2018
Trial design	Single group assignment, open label study
Population	- N = 14 - Osteomalacia in adults with XLH - Adults aged 18 to 65 years old
Intervention(s)	- 1.0mg/kg burosumab administered by subcutaneous injection monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90mg
Comparator(s)	No comparator
Outcome(s)	- Percent change from baseline in osteoid volume/bone volume at week 48 [time frame: baseline, 48 weeks] For full list of outcomes, see trial registry
Results (efficacy)	After 48 weeks of treatment, there was a significant improvement in all osteomalacia-related histomorphometric measures, including a decrease in osteoid volume/bone volume from 26.1%±12.4% at baseline to 11.9%±6.6% at week 48 (mean percentage change, -54%; *P* <.0001). Osteoid thickness decreased from 17.2±4.1 µm at baseline to 11.6±3.1 µm at week 48 (mean percentage change, -32%; *P* <.0001). Osteoid surface/bone surface also decreased from 92%±3% at baseline to 68%±14% at week 48 (mean percentage change, -26%; *P* =.0002)[19,20] When averaged across the midpoint of the dose intervals through week 24, the mean serum phosphorus concentration was above the lower limit of normal in 13 participants (mean concentration, 3.3±0.4 mg/dL), with a mean increase of 1.1 mg/dL from baseline. This increase in serum phosphorus was maintained through week 48 when measured at the end of the dose cycle between weeks 24 and 48 [19,20] At week 48, there was also evidence of increased bone remodelling markers, with a least squares mean increase of 77% (*P* <0.0001) in procollagen type 1 N-terminal propeptide (P1NP) and of 36% (*P* <0.0001) in C-terminal telopeptide of type 1 collagen (CTX) [19,20]
Results (safety)	Most patients (n = 10) experienced at least one burosumab-related adverse event, most commonly urticarial, pain or reaction at the injection site; abdominal pain; asthenia. Two patients experienced serious adverse events, including paraesthesia and migraine, but neither was considered related to burosumab, and both resolved. No deaths or incidents of hyperphosphataemia occurred [19,20]

Trial	NCT02526160, A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study With Open-Label Extension to Assess the Efficacy and Safety of KRN23 in Adults With X-linked Hypophosphatemia (XLH) **Phase III - completed** **Locations:** Europe (including the UK), USA and other countries **Study completion date:** December 2018
Trial design	Randomised, crossover assignment, quadruple masked study
Population	- N = 134 - X-linked hypophosphataemia - Adults aged 18 to 65 years old
Intervention(s)	- 1mg/kg administered subcutaneously every 4 weeks, for the duration of the study
Comparator(s)	- Placebo administered subcutaneously every 4 weeks through week 24, followed by burosumab 1mg/Kg for the duration of the study
Outcome(s)	- Percentage of participants achieving mean serum phosphorous levels above the lower limit of normal (2.5mg/dL [0.81mmol/L]) at the mid-point of the dose interval, as averaged across dose cycles between baseline and week 24 [time frame: baseline up to 24weeks and also up to 48 weeks][21] For full list of outcomes, see trial registry
Results (efficacy)	Burosumab significantly improved serum phosphorus, fracture/pseudo-fracture healing, stiffness, and physical functioning. Serum phosphorus was maintained with long-term burosumab treatment for up to 48 weeks, with no evidence of loss of effect in adults with XLH.[21] Burosumab dose reductions effectively managed mild hyperphosphatemia. There were no meaningful changes in ectopic mineralization. There were no neutralizing antibodies [22]
Results (safety)	No treatment-emergent adverse events led to study or treatment withdrawal. Frequency, severity, and types of AEs reported were consistent with previous burosumab trials [22]

Trial	NCT02312687, A Phase 2b, Open-Label, Long-Term Extension Study to Evaluate the Safety and Pharmacodynamics of KRN23 in Adult Subjects With X-Linked Hypophosphatemia (XLH) **Phase IIb** **Location:** USA **Study completion date:** November 2018
Trial design	Single group assignment, open label study
Population	- N = 20 - X-linked hypophosphataemia - Children, adults, older adults
Intervention(s)	- Burosumab subcutaneous (SC) injections every 4 weeks. Starting doses will be based on the subject's last dose in study NCT02312687 or NCT01571596

	Doses may be titrated to achieve the target peak serum phosphorus range
Comparator(s)	No comparator
Outcome(s)	Number of participants with adverse events (AEs), treatment emergent AEs (TEAEs), serious AEs (SAEs), and AEs Leading to discontinuation or death [time frame: screening through the end of study plus 4-8 weeks. The mean duration of burosumab exposure was 165.6 weeks (range: 68-184 weeks)] For full list of outcomes, see trial registry
Results (efficacy)	-
Results (safety)	-

Trial	NCT01340482, A Phase I/II, Open-Label, Repeat-Dose, Dose-Escalation Study of KRN23 in Adult Subjects With X-Linked Hypophosphatemia **Phase I/II - completed** **Locations:** USA and Canada **Study completion date:** October 2013	NCT01571596, An Open-Label, Long-Term, Extension Study to Evaluate the Safety and Efficacy of KRN23 in Adult Subjects With X-Linked Hypophosphatemia **Phase I/II - completed** **Locations:** USA and Canada **Study completion date:** June 2014
Trial design	Single group assignment, open label study	Single group assignment, open label study
Population	- N = 29 - X-linked hypophosphataemia - Adults aged 18 years old and over	- N = 23 - X-linked hypophosphataemia - Adults aged 18 years old and over
Intervention(s)	- Escalating doses of burosumab (0.05, 0.10, 0.30 and 0.60mg/kg) administered subcutaneously every 28 days (up to 4 doses)	- Escalating doses of burosumab (0.05, 0.10, 0.30, and 0.60 mg/kg) administered subcutaneously every 28 days (up to 12 doses)
Comparator(s)	No comparator	No comparator
Outcome(s)	- Safety and efficacy of repeated subcutaneous injections of burosumab [time frame: on-treatment: 6.5months, 27 total visits] For full list of outcomes, see trial registry	- Safety and efficacy of repeated subcutaneous injections of burosumab [time frame: 13.5 months, (50 visits)] For full list of outcomes, see trial registry
Results (efficacy)	The area under the effect concentration-time curve (AUECn) for change from baseline in TmP per glomerular filtration rate, serum Pi, 1,25(OH)2 D, and bone markers for each dosing interval increased linearly with increases in burosumab AUCn . Linear	Monthly burosumab significantly increased serum inorganic phosphorus (Pi), TmP/GFR (renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate), and 1,25$(OH)_2$D (dihydroxyvitamin D) n all subjects. Burosumab has the potential to improve biochemical and skeletal

	correlation between serum burosumab concentrations and increase in serum Pi support burosumab dose adjustments based on pre-dose serum Pi concentration[23]	outcomes in adults and children with XLH, with greater convenience and compliance than multiple daily doses of calcitriol and phosphate.[24]
Results (safety)	-	KRN23 had a favourable safety profile[24]

ESTIMATED COST

The list price of burosumab in England is £2,992 per 10 mg/mL vial, £5,984 per 20mg/mL vial and £8,976 per 30mg/mL vial. [7]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Highly Specialised Technologies Guidance. Burosumab for treating X-linked hypophosphataemia in children and young people. [HST8]. October 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- Haffner *et al.* Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. 2019.[5]

ADDITIONAL INFORMATION

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