

HEALTH TECHNOLOGY BRIEFING JANUARY 2021

Burosumab for tumour-induced osteomalacia

NIHRIO ID	11027	NICE ID	10507
Developer/Company	Kyowa Kirin Ltd	UKPS ID	658721

Licensing and market availability plans	Currently in Phase II clinical trials.
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SUMMARY

Burosumab is in clinical development for the treatment of adults with tumour-induced osteomalacia (TIO). TIO is a rare disease where an overproduction of FGF23 leads to renal phosphate wasting and low levels of phosphate and vitamin D in the body. This causes weakening (or softening) of bones. Main symptoms include bone pain, muscle weakness/fatigue and fractures and without a timely diagnosis, TIO can lead to a significant decrease in quality of life, severe functional impairment and even prostration.

Burosumab is administered by subcutaneous injection. Burosumab is designed to recognise and attach to a protein called FGF23. By attaching to the FGF23 protein, burosumab blocks its activity, thus restoring phosphate and vitamin D levels by achieving phosphate homeostasis. If licensed, burosumab will provide a treatment option for TIO.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Treatment of adults with tumour-induced osteomalacia (TIO).^{1,2}

TECHNOLOGY

DESCRIPTION

Burosumab (Crysvita[®], KNR23) is a fully human immunoglobulin 1 (IgG1) monoclonal antibody to FGF23.³ By binding to FGF23, burosumab inhibits FGF23 signalling, thereby increasing renal 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 bone disease is decreased.⁴

Burosumab is in clinical development for the treatment of TIO. In two phase II clinical trials (NCT02304367, NCT02722798), adults received burosumab at a weight based starting dose of 0.3mg/kg administered subcutaneously (SC) every 4 weeks (Q4W). Doses may have been titrated up to achieve fasting peak serum phosphate level within the target range of 2.5 to 4.0mg/dL.^{1,2}

INNOVATION AND/OR ADVANTAGES

There are no approved pharmacological treatments that target the underlying pathophysiology of TIO, which is phosphate wasting. The treatment of choice for TIO is resection of a tumour with a wide margin to ensure complete tumour removal, as recurrences of these tumours have been reported.^{5,6} When surgery is not possible, pharmacological treatment includes supplementation with oral phosphate and active vitamin D; however, oral phosphate is associated with tolerability issues and severe side effects.^{6,7} As tumours can arise in bone or soft tissue, occur from head to toe and are typically very small in size and slow-growing, locating these tumours is often quite challenging.⁸ Due to the location of the tumours, surgery can also be inappropriate.⁶

Burosumab is the first drug that directly targets FGF23 which reduces serum levels of phosphate by regulating phosphate excretion and vitamin D activation in the kidney. By blocking excess activities of FGF23, burosumab restores phosphate reabsorption by the kidney and increases the activation of vitamin D, which enhances intestinal absorption of phosphate.⁹

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Burosumab is currently licensed in the EU/UK for the treatment of X-linked hypophosphataemia (XLH), in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.¹⁰

The most common adverse drug reactions in adult patients include back pain, headache, tooth infection, restless legs syndrome, muscle spasms, vitamin D decrease and dizziness.¹⁰

Burosumab is also in phase III and II clinical development for the treatment of various XLH indications, cutaneous skeletal hypophosphataemia syndrome and epidermal nevus syndrome.¹¹

PATIENT GROUP

DISEASE BACKGROUND

TIO is an extremely rare paraneoplastic syndrome clinically characterised by bone pain, fractures and muscle weakness. It is caused by tumoral overproduction of FGF23 that acts primarily at the proximal renal tubule decreasing phosphate reabsorption and 1,25(OH)₂D, thus producing hypophosphatemia and osteomalacia.¹² Overproduction of FGF23 levels results in a similar biochemical profile to XLH that includes low serum phosphate, phosphaturia, an abnormal tubular maximum reabsorption rate of phosphate to glomerular filtration rate, elevated alkaline phosphatase, normal calcium, and low to normal levels of 1,25(OH)₂D.¹³ Most tumours that cause TIO are small, slow-growing known as phosphaturic mesenchymal tumours. These tumours most commonly occur in the skin, muscles, or bones of the extremities or the paranasal sinuses around the head.¹⁴ Most of these tumours are benign, meaning they are not associated with cancer.¹⁵

TIO is caused by the development of a tumour that releases FGF23. However, the exact causes for the development of the tumours associated with TIO are unknown. It is most likely that these tumours develop by chance.¹⁵ TIO typically occurs in adults with equal gender distribution.¹² The symptoms of TIO include fatigue, muscle weakness, bone pain, fractures, and weakening of the bones.¹⁵ The duration of symptoms before diagnosis is quite variable but averages about 2.5 years.¹⁶

CLINICAL NEED AND BURDEN OF DISEASE

Approximately 500 cases of TIO have been reported worldwide. Based on the published case reports, the average age of diagnosis is 40–45 years indicating that adults may be more vulnerable to this disease,¹⁷ but TIO has also been reported in children.^{14,18-20}

In England (2019-20), there were 4 finished consultant episodes (FCE) and 3 admissions with a primary diagnosis of other adult osteomalacia (ICD-10 code M83.8) resulting in 7 FCE bed days and 2 day cases.²¹

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

A stepwise approach is recommended, starting with a thorough medical history and physical examination, followed by functional imaging of the entire body, including extremities. Suspicious lesions should be confirmed by anatomical imaging, and if needed, selective venous sampling with measurement of FGF23 (if required to confirm suspicious lesion is the phosphaturic mesenchymal tumours secreting FGF23).¹² It has been suggested that definitive treatment of TIO is further delayed by an average of 5 years after diagnosis due to inability to find the underlying tumours.²²

The first treatment option is complete resection of the tumour with wide margins. Surgery is considered the only definitive treatment.^{12,18,23} Sometimes complete resection is not possible, and tumours may be located in difficult to access areas, or where surgery would likely introduce significant morbidity. Image-guided ablation with radiofrequency or cryoablation is a promising alternative for this group of patients, with little morbidity and short hospital stays.^{12,16,24,25}

CURRENT TREATMENT OPTIONS

There are currently no approved treatment options for TIO. When it is not possible to detect and/or completely resect the tumour, oral phosphate and active vitamin D (calcitriol or alfacalcidol) supplementation is the mainstay of treatment, to improve symptoms and heal osteomalacia, while maintaining phosphatemia in the lower end of the normal range, and parathyroid hormone and alkaline phosphatase in the normal range.^{12,18} Medical treatment should be continued for as long as the tumour is not identified or resected.²⁶

Treatment with oral phosphate is frequently limited by the presence of gastrointestinal symptoms, such as abdominal pain and diarrhoea and side effects such as nephrocalcinosis, reduced kidney function, and hyperparathyroidism.^{6,7,12}

PLACE OF TECHNOLOGY

If licensed, burosumab will provide a treatment option for adults with TIO.

CLINICAL TRIAL INFORMATION

Trial	NCT02304367; A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23, an Antibody to FGF23, in Subjects with Tumor-Induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS)-Associated Osteomalacia Trial phase II – Completed Location(s): USA Primary completion date: July 2017
Trial design	Single group assignment, open label
Population	N=14; aged ≥ 18 years; TIO-associated osteomalacia based on evidence of excessive FGF23 that was not amenable to cure by surgical excision of the underlying tumour/lesion
Intervention(s)	Burosumab at a starting dose of 0.3 mg/kg administered SC Q4W. Doses may have been titrated up in order to achieve fasting peak serum phosphate levels within the target range of (0.81-1.29mmol/L (2.5 to 4.0 mg/dL)
Comparator(s)	No comparator
Outcome(s)	Co-primary endpoints: <ul style="list-style-type: none"> Percentage of participants achieving mean serum phosphate levels above 0.81 mmol/L (2.5 mg/dL) at

	<p>the mid-Point of the dose intervals between baseline and week 24 [Time frame: mid-point of each dose interval from baseline to week 24 (weeks 2, 6, 10, 14 and 22 [there was no study visit at week 18])]</p> <ul style="list-style-type: none"> • Change from baseline to week 48 in excess osteoid thickness, osteoid surface/bone surface, osteoid volume/bone volume, and mineralisation lag time (Time frame: baseline, week 48) <p>See trial record for the full list of other outcomes</p>
Results (efficacy)	<ul style="list-style-type: none"> • Seven (50%) patients achieved a mean serum phosphate above the lower limit of normal (0.81 mmol/L) (at week 22, 12 (86%) patients achieved a fasting serum phosphorus level ≥ 0.81 mmol/L)¹³ • Most measures of osteomalacia related histomorphometric measures were improved at Week 48 including osteoid thickness, osteoid volume/bone volume, and mineralisation lag time; osteoid surface/bone surface showed no change¹³ • Overall, patients showed an improvement in physical mobility with burosumab¹³ • Patients reported a reduction in pain and fatigue and an increase in physical health¹³
Results (safety)	<ul style="list-style-type: none"> • Burosumab was generally well tolerated. There were 16 serious AEs in seven patients; none were considered related to burosumab¹³

Trial	<p>NCT02722798; A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23 in Patients With Tumor-Induced Osteomalacia or Epidermal Nevus Syndrome</p> <p>Trial phase II – Completed</p> <p>Location(s): Japan and Korea</p> <p>Primary completion date: July 2017</p>
Trial design	Single group assignment, open label
Population	N=13; aged ≥ 18 years; TIO-associated osteomalacia not amenable to receive surgical excision of the offending tumour/lesion
Intervention(s)	Burosumab was administered SC Q4W with the initial dose being 0.3 mg/kg. According to the dose adjustment criteria, the doses of burosumab at weeks 4, 8, 12, and 16 were adjusted based on the serum phosphate level obtained 2 weeks before administration (at weeks 2, 6, 10, and 14 respectively). At and after week 20, the dose of burosumab was set at the same level as at week 16. The dose increment from the preceding administration was set at 0.2 mg/kg and the maximum dose, at 2.0 mg/kg. ²⁷
Comparator(s)	No comparator

Outcome(s)	<p>Primary endpoint</p> <ul style="list-style-type: none"> • Serum phosphate concentration at each test time point <p>See trial record for the full list of other outcomes.</p>
Results (efficacy)	<ul style="list-style-type: none"> • Mean serum phosphate levels increased and remained consistently above the lower limit of normal and in the normal range from week 14 to week 112²⁷ • All metabolic bone markers initially increased after the start of burosumab administration. They reached maximum values at week 16 or 24 and then gradually decreased²⁷ • Bone biopsy data were poor, therefore no notable change was observed in osteoid thickness, osteoid/bone surface, and osteoid/bone volume²⁷ • Overall, the patients' physical mobility improved after the start of burosumab administration²⁷
Results (safety)	<ul style="list-style-type: none"> • Burosumab was generally well tolerated, with no treatment - related AEs of grade ≥ 3 and no treatment-related serious AEs²⁷

ESTIMATED COST

The list price of burosumab solution for injection is £2,992 per 10mg/ml vial, £5,984 per 20mg/ml vial and £8,976 per 30 mg/ml vial.²⁸

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- No relevant guidance identified.

ADDITIONAL INFORMATION

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