SMC2588

burosumab solution for injection (Crysvita®)

Kyowa Kirin Ltd

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The Scottish Medicines Consortium (SMC) has completed its reassessment of the evidence for the above product using the ultra-orphan framework:

Advice: following reassessment through the ultra-orphan framework

burosumab (Crysvita®) is accepted for use within NHSScotland.

Indication under review: for the treatment of X-linked hypophosphataemia in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease.

In an open-label, randomised, phase III study in patients aged 1 to 12 years with X-linked hypophosphataemia, there was a significantly greater improvement in rickets, assessed by the Radiographic Global Impression of Change global score at week 40, in the burosumab group compared with the conventional therapy group (oral phosphate and vitamin D).

In addition, the company provided further data from extension phases of the main studies and some supportive observational data on the use of burosumab in patients with X-linked hypophosphataemia.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical context

1.1. Background

Burosumab is the first disease-modifying biologic treatment to target the pathophysiology of X-linked hypophosphataemia. It is a recombinant human monoclonal antibody (IgG1) that inhibits the activity of fibroblast growth factor 23 (FGF23), thereby increasing tubular reabsorption of phosphate from the kidney and increasing serum concentration of 1, 25 dihydroxy-vitamin D. The aim of treatment is to achieve normal serum phosphate levels and therefore decrease the clinical consequences of X-linked hypophosphataemia.[1, 2]

Burosumab initially received a conditional marketing authorisation 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. Burosumab was validated as an ultra orphan medicine by SMC and underwent initial assessment using the ultra orphan framework in February 2020 (SMC2240) and has since been available within the ultra orphan pathway. In 2020, the conditional marketing authorisation was extended to include adults, which is being considered separately by SMC (SMC2514), and to remove the need for children to have growing skeletons to: the treatment of X-linked hypophosphataemia, in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults. In October 2022, the conditional marketing authorisation was converted to a full marketing authorisation by the Medicines and Healthcare Products Regulatory Agency (MHRA).

The recommended starting dose of burosumab in children and adolescents aged 1 to 17 years is 0.8 mg/kg given as a subcutaneous injection every 2 weeks with the dose adjusted according to fasting serum phosphate levels; maximum recommended dose is 90 mg.[1]

1.2. Nature of condition

X-linked hypophosphataemia is a rare genetic condition. Affected patients have inactivating mutations in the phosphate-regulating gene with homologies to endopeptidases on the X-chromosome (PHEX) which alters phosphate sensing and increases serum FGF23 leading to increased renal phosphate excretion, reduced vitamin D production, and subsequent hypophosphataemia. X-linked hypophosphataemia is a chronic, progressive, debilitating, multisystem condition that severely impacts day to day functioning and health-related quality of life. Patients with X-linked hypophosphataemia have skeletal abnormalities and the main clinical consequences in children are rickets, lower limb deformities, growth retardation and disproportionately short stature. Patients may also have symptoms such as dental abscesses, hearing loss, headaches, muscle weakness, pain, stiffness and fatigue.[2, 3]

Patients have mobility problems and may be unable to participate in activities such as sports which, along with an altered physical appearance, have a negative psychological impact, particularly on children. Due to the genetic nature of the condition, family members may also be affected meaning the caregiver could also be suffering from the condition further increasing the family burden. In a significant proportion of patients surgery is required to correct skeletal

deformities, which would require time off school and impact on learning and potential career options.

Prior to the availability of burosumab, patients with X-linked hypophosphataemia received conventional treatment with phosphate and vitamin D supplements. While early treatment can improve rickets, severe skeletal abnormalities usually remain, and phosphate and vitamin D do not treat the underlying condition. Adherence to therapy is difficult due to need for frequent dosing of phosphate supplements (often 4 to 6 times a day) and adverse effects such as gastrointestinal symptoms. Vitamin D can result in hypercalcaemia and kidney stones. In addition, conventional therapy further stimulates FGF23 production, which may limit efficacy.

1.3 Category for decision-making process

Eligibility for a PACE meeting. Burosumab meets SMC ultra-orphan criteria

2. Impact of new technology

Comparative efficacy

Key evidence for this indication is from the CL301 study. Details are summarised in Table 2.1.

Table 2.1 Overview of relevant study[1, 4]

Criteria	CL301
Study design	Multicentre, randomised, open-label, phase III study
Eligible patients	- X-linked hypophosphataemia with confirmed PHEX mutation or family member with appropriate X-linked dominant inheritance. - aged 1 to 12 years - Thacher rickets severity score (RSS) ≥2.0 - fasting serum phosphorus <0.97 mmol/L - conventional treatment for ≥6 months (if <3 years old) and ≥12 months (if >3 years old)
Treatments	Treatments were commenced after a seven-day washout of conventional therapy: - burosumab was initiated at 0.8 mg/kg subcutaneously every 2 weeks, increased to 1.2 mg/kg every 2 weeks if two consecutive pre-dose, fasting, serum phosphorus concentrations were <1.03 mmol/L and serum phosphorus had increased by <0.16 mmol/L from baseline on a single measurement - conventional therapy resumed and comprised oral phosphate (20 to 60 mg/kg per day divided doses) and alfacalcidol (40 to 60 nanograms/kg per day) or calcitriol (20 to 30 nanograms/kg per day) titrated on the basis of published recommendations.
Randomisation	Ratio of 1:1 stratified by Thacher RSS (≤2.5 versus >2.5), age (<5 versus ≥5 years) and region (Japan versus rest of the world).
Primary outcome	Change in severity of Rickets at week 40, assessed using the Radiographic Global Impression of Change (RGI-C) global score (7-point ordinal scale with scores of -3=severe worsening to +3=complete healing), based on skeletal abnormalities on wrist and knee radiographs assessed by three independent paediatric radiologists.
Secondary outcomes	Change in severity of Rickets (RGI-C global score) at week 64 At week 40 and 64 the following were assessed:

	- Proportion of patients with RGI-C global score ≥2.0 - Lower limb deformity assessed by RGI-C of long leg radiographs - Thacher RSS (range 0 [no rickets] to 10 [severe rickets] based on sum of scores for the most severely affected wrist [0 to 4] and knee [0 to 6]). - Change from baseline in recumbent length/standing height Z score - Percent of predicted normal 6-minute walking test (in those aged ≥5 years at screening)
Statistical analysis	The study was not controlled for type I error in the secondary outcomes, no hierarchy was reported.

Patients in the burosumab group had significantly greater improvement in rickets as assessed by the Radiographic Global Impression of Change (RGI-C) global score at week 40 compared with those in the conventional therapy group and this was maintained at week 64. Details of primary and selected secondary outcomes, which favoured burosumab over conventional therapy, are presented in Table 2.2. Phosphate levels of patients in the burosumab group increased to the lower limit of normal whereas there were minimal changes in the conventional therapy group.[4]

Table 2.2 Primary outcome (week 40) and selected secondary outcomes (week 64) from study CL301.[1, 4]

		Burosumab (n=29)	Conventional therapy (n=32)	Difference (95% confidence interval)
LS mean Radiographic Global Impression of Change global score at week 40[a]		1.9	0.8	1.1 (0.8 to 1.5) p<0.001
Proportion of patients with Radiographic Global Impression of Change global score ≥2.0 at week 40		72%	6.2%	Odds ratio:39 (7 to 212)
LS mean Radiographic Global Impression of Change global score at week 64[a]		2.1	1.0	1.0 (0.7 to 1.3)
LS mean total Thacher rickets severity score	Baseline	3.2	3.2	
	Change at week 64	-2.2	-1.0	-1.2 (-1.6 to -0.8)
LS mean Radiographic Global Impression of Change lower limb deformity score at week 64[a]		1.3	0.3	1.0 (0.6 to 1.4)
LS mean recumbent length and standing height Z score	Baseline	-2.32	-2.05	
	Change at week 64	0.17	0.02	0.14 (0 to 0.29)
	Baseline	65%	76%	

Mean percent predicted normal in 6 minute walk test[b]	Change at week 64	9%[c] (n=13)	2%[c] (n=20)	7% (0.01 to 14.5)

CI: confidence interval, LS: least squares, N/A: not applicable, [a]provides one score therefore no baseline measurement, [b]performed in patients aged ≥5 years at screening and able to complete, [c]adjusted for baseline differences

Health-related quality of life (HRQoL) was measured in study CL301 in patients aged ≥5 years at screening using the following secondary and exploratory outcomes. Results for the Patient Reported Outcomes Measurement Information System (PROMIS), domains of pain interference, physical function mobility and fatigue favoured burosumab compared with conventional therapy. Pain intensity assessed using the Faces Pain Scale - Revised (FPS-R) indicated that the majority of patients reported no pain on at baseline and at each study visit in both treatment groups. The SF-10 health survey for children indicated mild impairment at baseline and there were improvements in the physical health domain in the burosumab group at week 40 and 64 compared with baseline, whereas improvements were smaller in the conventional therapy group.[5]

Patients who completed the 64-week, active-controlled period were eligible to enter the extension phase and receive up to an additional 76 weeks of open-label burosumab. Twenty-five patients originally randomised to burosumab continued treatment and 26 patients switched from conventional treatment to burosumab. Patient numbers decreased during the extension due to commercially available burosumab. Results to week 88 indicate that the treatment effects on RGI-C global score, RSS, RGI-C lower limb deformity, height and 6-minute walk test were maintained.[6, 7] Improvements in HRQoL were maintained to week 88 in eligible patients who continued to receive burosumab in the extension phase (n=12) and were noted for PROMIS domains of pain interference, physical function mobility and fatigue in those patients who switched from conventional therapy to burosumab (n=14).[8]

Published post hoc analysis of outcomes at week 64 in study CL301 explored the efficacy and safety of burosumab versus conventional therapy in younger (<5 years, n=26) and older (5 to 12 years, n=35) children with X-linked hypophosphataemia and found similar improvements in outcomes that assessed rickets and height in both age groups.[9]

Study CL201

CL201 was an open-label, phase II study that recruited children aged 5 to 12 years of age with a diagnosis of X-linked hypophosphataemia (n=52). Eligible patients had active rickets at growth plates, bowing of the femur or tibia, or both and their pubertal stage was classified as Tanner stage 2 or lower. The final 16 recruited patients were required to have a Thacher RSS of at least 1.5 at the knee. They were randomly assigned equally to receive subcutaneous burosumab, at an initial dose of either 0.1 mg/kg to 0.3 mg/kg every 2 weeks (n=26) or 0.2 mg/kg to 0.6 mg/kg every 4 weeks (n=26). The dose was adjusted to achieve a serum phosphorus level at the low end of the normal range. The primary outcome, change in Thacher RSS, was -1.1 and -0.7 at

week 40 in the 2-weekly and 4-weekly dosing groups respectively (p<0.001 for both comparisons). The RGI-C global score at week 40 was 1.6 in both groups. These results indicated improvements in rickets in both groups at week 40 and this was maintained at week 64.[2, 10] Improved functional ability and decreased pain, as assessed by the Paediatric Orthopaedic Society of North America – Paediatric Outcomes Data Collection Instrument (POSNA-PODCI) questionnaire, was shown in the overall population at 64 weeks. This study included a 96-week extension phase. All patients continued into the extension phase and received burosumab every 2 weeks. Results to week 160 indicated that the treatment effect on knee RSS was maintained and RGI-C global score continued to improve.[1, 11]

Study CL205

Study CL205 was an open-label, single-arm, phase II study that recruited children aged 1 to 4 years of age with X-linked hypophosphataemia (n=13). At least five patients were required to have a Thacher RSS at the knee of at least 1.5 at screening. Patients received burosumab 0.8 mg/kg by subcutaneous injection every 2 weeks increased to 1.2 mg/kg every 2 weeks if two consecutive pre-dose serum phosphorus concentrations were below 1.03 mmol/L, serum phosphorus had increased by <0.16 mmol/L from baseline, and a dose had not been missed. Treatment continued for 160 weeks. Safety and change from baseline to week 40 in fasting serum phosphorus concentration were the co-primary outcomes. The mean fasting serum phosphorous concentration increased from 0.81 mmol/L to 1.12 mmol/L. The least squares mean increase from baseline to week 40 of 0.31 mmol/L was significant, p<0.001. Total Thacher RSS decreased by least squares mean of -2.0 from baseline to week 64. The RGI-C least squares mean score was +2.2 at week 64 also indicating improvement.[12] In addition, all patients achieved substantial healing of rickets (defined as a RGI-C score ≥+2.0) by week 40. Patients who completed study CL205 to week 64 were eligible to enter the 96-week extension phase and, in 12/13 patients who entered and completed to week 160 weeks, the improvements in outcomes that assessed rickets were maintained.[1, 13]

Additional evidence on reassessment

Following the initial assessment in February 2020 (SMC2240) the company had the opportunity to collect additional data to support its submission. This included information from studies as well as real world data collection.

Longer term follow up from the extension phases of the main and supportive studies have been presented which suggest that the treatment effect is maintained.

The submitting company has provided some additional supportive real-world data on the use of burosumab in patients with X-linked hypophosphataemia. This includes some limited data on longer term treatment to 3 years and also in patients aged ≥12 years which indicates that the biochemical effects of burosumab are maintained as well as improvements in RSS and RGI-C. This also includes some limited data from Japan suggesting improvements were achieved in patients with less severe disease (RSS <2.0).[1, 13-24]

The submitting company has provided additional quality of life data from an observational study in 32 children and adolescents (≥4 to <18 years) with X-linked hypophosphataemia and growing skeletons from the UK X-Linked Hypophosphataemia Registry; the majority of patients were receiving burosumab. Assessments were made, according to RSS score where possible, using the EuroQol-5 dimension-Youth (EQ-5D-Y) which is a child friendly version of the generic quality of life measure and the Child Health Utility 9 Dimensions (CHU-9 D). Results remained similar at baseline and 6 months. The company considered that the available results do not contradict derived utility scores used in the original submission.[25]

Comparative safety

In study CL301, treatment emergent adverse events were reported in 100% (29/29) of patients in the burosumab group and 84% (27/32) of patients in the conventional therapy group. Adverse events were considered related to study treatment in 59% (17/29) and 22% (7/32) of patients respectively. No serious, treatment-related adverse events were reported. Grade 3 or 4 adverse events occurred in 14% (4/29) and 9.4% (3/32) of the respective groups. There were no adverse events leading to study discontinuation, treatment discontinuation or death.[4]
The most common adverse events were pyrexia (55% and 19%), cough (52% and 19%), arthralgia (45% and 31%), vomiting (41% and 25%), nasopharyngitis (38% and 44%), pain in extremities (38% and 31%), headache (34% and 19%), injection site erythema (31% and 0), dental caries (31% and 6%), tooth abscess (28% and 9%), rhinorrhoea (24% and 6%), diarrhoea (24% and 6.2%) and vitamin D decrease (21% and 3.1%).[4] Pre-defined adverse events of interest that occurred more commonly in the burosumab group compared with conventional therapy included injection site reaction (52% and 0) and hypersensitivity (38% and 19%). No patients in either group developed hyperphosphataemia. There were minimal changes in plasma intact parathyroid hormone, serum calcium, urine calcium excretion or nephrocalcinosis scores in both groups.[4]

There were no new safety concerns from the extension phase.

Clinical effectiveness issues

The key strengths and uncertainties of the clinical case are summarised below.

Key strengths:

- In the key phase III study, CL301, patients in the burosumab group had significantly greater improvement in rickets, as assessed by the RGI-C at week 40, compared with those in the conventional therapy (oral phosphate and vitamin D) group. Improvement was maintained at week 64 and during the extension phase to week 88.[1, 4]
- In addition, substantial healing of rickets, defined as a RGI-C global score ≥2, was achieved by 72% of the burosumab group compared with 6.2% of the conventional therapy group.[2, 4]
- Greater improvements with burosumab versus conventional therapy were demonstrated for the key secondary outcomes at week 64 including change in Thacher

RSS and RGI-C lower limb deformity score. In addition, burosumab was associated with greater improvements in growth (standing height/recumbent length) and walking ability (percent predicted of normal for 6-minute walk test).[4]

- In CL301, quality of life assessing pain interference, physical function mobility and fatigue numerically favoured burosumab compared with conventional therapy at weeks 40 and 64.[5]
- Additional real-world data were provided to support improvement in biochemical and clinical outcomes in patients following longer term treatment (up to 3 years), in adolescents aged 13 to 17 years and in patients with less severe disease (RSS <2.0).
- Clinical experts consulted by SMC viewed burosumab as a therapeutic advancement. They note that it has become an established therapy since its introduction via the ultra orphan pathway and that it is very helpful to control rickets, especially in difficult cases. Patients are happy to receive burosumab and do not wish to change to previous conventional therapy.

Key uncertainties:

- X-linked hypophosphataemia is a chronic lifelong condition. However, data on the impact of burosumab on the long-term consequences of X-linked hypophosphataemia are not available.
- Controlled data demonstrate a treatment effect of burosumab on correction of bone defects in childhood, but it is unclear how this would affect progression of bone disease into adulthood, patient-relevant outcomes and impact on quality of life.
- While some short-term controlled data on quality of life are available from study CL301, the magnitude of effect and clinical relevance of improvements are difficult to interpret and may be limited by the open-label nature of the study. When pain was assessed by FPS-R, a measure that has not been specifically validated in X-linked hypophosphataemia, patients had no pain at baseline, suggesting that it may not be a reliable assessment in this population.[5]
- Burosumab is licensed for use in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease. While the extension phase of studies CL201 and CL301 included some patients slightly older than 12 years, no clinical trial evidence in patients who commence treatment between the ages of 13 to 17 years is available. It is possible this group may respond differently due to puberty and bone maturity. Additional real-world data in adolescents ≥12 years indicate improvements with burosumab but are uncontrolled and limited by small numbers and heterogeneity.
- Only patients with total Thacher RSS of at least two were recruited to study CL301. Patients with milder severity of X-linked hypophosphataemia (Thacher score of at least 1.5) were included in phase II studies, however there is no comparative evidence versus conventional therapy in these patients. Additional uncontrolled data in patients with

less severe disease from Japan, indicate improvements with burosumab but patient numbers were limited.

- Small patient numbers were included in the key study, although, it is acknowledged that X-linked hypophosphataemia is a rare condition and burosumab is an ultra-orphan medicine, therefore small patient numbers are inevitable.
- There are no data of the effects of stopping burosumab treatment or on retreating previously treated patients on serum phosphate levels and skeletal outcomes.

Overall, the clinical case was considered reasonable in the short-term when burosumab is likely to provide improvement of rickets in children and adolescents with X-linked hypophosphataemia. However, due to the limited data, there remains some uncertainty about efficacy in patients aged between 13 and 17 years, the effect on progression of bone disease into adulthood and on the long-term consequences of X-linked hypophosphataemia. The impact on patients and families in the longer term remains unclear.

3. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of burosumab, as an ultra-orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- X-linked hypophosphataemia (XLH) is a progressive, life-long disease that affects children's growth. They suffer symptoms of bone pain, muscle weakness and fatigue which may impair normal activities and restrict the child's ability to fully join their peers in normal life. Invasive procedures such as orthopaedic surgery may be needed to correct resulting bone deformities. The disease and its conventional treatment have a significant impact on patient's daily living, education, employment and social relationships and there is a substantial physical, emotional and social burden for patients and their families.
- Conventional therapy comprises a heavy and disruptive burden often requiring four or more doses of phosphate daily. Biochemical control and tolerability are poor and compliance is difficult. There is an unmet need for an effective treatment providing better phosphate control, reduced symptoms and complications needing surgery, with easier dosing. Burosumab offers the first and only disease modifying treatment for XLH and fills an unmet need for these children.
- PACE participants considered that burosumab for the treatment of children with XLH, offered transformative potential with improved quality of life. By reducing symptoms and complications, burosumab may allow patients to lead a more normal life, enjoy education, physical activities and employment leading to improved physical and

emotional well-being.

- PACE clinicians highlighted their experience of good biochemical control achieved in treated patients. Patients may experience reduced symptoms including pain, weakness and fatigue. They may achieve normal growth and reduce the severity of rickets, leading to fewer complications of bone deformities and less need for corrective surgery and joint replacement, which can be complex, painful and require a long recovery period.
- While burosumab requires administration by subcutaneous injection every 2 weeks, which may be expected to be less desirable for children, experience from PACE participants noted that it had been simple to deliver, suggesting how poorly accepted oral conventional therapy has been. Although some children may experience injection-related discomfort or fear of having a jag every 2 weeks, the potential benefits of burosumab were considered to outweigh this as an issue.

Additional Patient and Carer Involvement

We received a patient group submission from XLH UK, which is a registered charity. XLH UK has not received any pharmaceutical company funding in the past two years. A representative from XLH UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

4. Impact beyond direct health benefits and on specialist services

Treatment with burosumab is expected to reduce skeletal deformities and potentially other symptoms such as pain and fatigue. This would have a positive impact on patients' attendance and performance at school, improve their ability to enter further education and increase their choice of employment. Patients may require less care, which would reduce the impact on family/carers, increasing their ability to work and participate in family activities. These wider benefits were not captured in the base case results of the economic evaluation submitted by the company, but an included scenario looked to capture the indirect improvements in carers health that burosumab may bring.

Administration is by subcutaneous injection every 2 weeks which may be preferable to complex multiple oral daily doses of phosphate and vitamin D but may have an administration impact on services. Clinical experts note that patients are required to attend hospital for monitoring and, initially, for administration of the injection. They advise that patients appear to be happy to be on burosumab, with none requesting to stop and change back to previous oral treatments.

The burden on NHS services beyond the initiation period is uncertain. The company has suggested that patients would transition to receiving burosumab at home, either through self-administration, carer administration or nurses administration. The extent to which nurses are required to administer burosumab on a continued basis was uncertain, but clinical experts

consulted by SMC noted that the demands on nurses' time for current burosumab patients in Scotland was significant.

5. Value for money

5.1. Economic case

The economic case is summarised in Table 5.1 below. The economic evaluation built on that used within the original submission (SMC2240). Relevant to the economic case, the company collected additional clinical data from extension phases of the CL201 and CL301 studies, real world evidence on the initiation of burosumab in older children and a new quality of life study in children with X-linked hypophosphataemia. None of these pieces of evidence were used directly in the modelling, but were presented as validating the modelling approach. In the absence of any updates, the base case economic results were the same as reported in SMC2240.

Table 5.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	93 years, based on a maximum age of 100 and a mean starting age of 7 years
Population	Children, aged 1 to 17, with XLH and radiographic evidence of bone disease
Comparators	Burosumab was compared with conventional therapy, which comprised of oral phosphate and vitamin D
Model description	The submission utilised a 5 state Markov model. Health states reflected patients' rickets severity, defined by RSS. These states were healed (RSS=0), mild (RSS=0.5-1.0), moderate (RSS=1.5-2.0) and severe (RSS=2.5-5.0). There was an additional absorbing death state. Patients could transition between each of the health states during each of the yearly cycles. Patients could move from each of the health states to death.
Clinical data	The main clinical data sources on burosumab were the CL201, CL205 and CL301 studies.[1, 4, 11, 13] These informed the transition probabilities. The main clinical data sources for the conventional therapy arm were the CL301 study as well as a UK retrospective records review. XLH is not associated with excess mortality, and so death was equalised to the age and sex matched general population mortality rate in Scotland.
Extrapolation	Transition probabilities were assumed constant until the age of 18. After that point, patients remained in that health state for the duration of the model.
Quality of life	No health related quality of life data suitable for estimating utilities were collected as part of the clinical studies. Instead, utility values were derived from a multi-stage vignette study.[26] Vignettes were developed through interviews with clinical experts. These described the quality of life for patients in the various health states across the different ages of 1-4yrs, 5-12yrs, 13-17yrs, 18 years, 40 years and 60 years. Subsequently, different clinical experts then estimated the expected EQ-5D-5L dimension scores for each of the vignettes. This resulted in a wide range of utility estimates from 0.91 (age 5-12, healed) to 0.282 (age 60, severe). A 'last observation carried forward' approach was used to estimate utilities between the adult ages, with age-adjustment applied. No disutilities were included for adverse events, disease complications or downstream surgical interventions. In scenario analysis, carer disutilities were included. A disutility of -0.08 was applied for each child in the severe and moderate state, up until the patient turned 18. The value of the disutility was estimated from parents in the US with one or more children with an activity limitation.[27]

Costs and resource use	Medicine acquisition costs were included for burosumab and conventional therapy. No administration costs were included for either treatment. Patients continued to receive burosumab until the age of 14 in females and 16 in males, after which no retreatment took place. Within the first year of burosumab treatment, patients were assumed to receive 5 blood tests administered by a nurse. Wider NHS costs included were for surveillance and monitoring, physiotherapy and orthopaedic interventions.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price.

5.2. Results

The base case results inclusive of the PAS discount on burosumab are presented in Table 5.2. The main driver of the increased costs is from the acquisition of burosumab. The main difference in quality adjusted life years (QALYs) is from the greater occupancy of the healed state by patients receiving burosumab.

Table 5.2 – Base case results (PAS discount on burosumab)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Burosumab	743,266	21.45	708,957	5.59	126,931
Conventional therapy	34,309	15.86	-	-	-

QALY: quality adjusted life year, ICER: incremental cost effectiveness ratio

5.3. Sensitivity analyses

To explore uncertainty the company conducted sensitivity analysis. This indicated that the model was sensitive to changes in the transition probabilities and the utility values, particularly the utility values for the healed state.

Additionally, the company has provided scenarios, exploring areas of structural uncertainty. These are presented in Table 5.3. The company provided a range of further scenario analyses using alternative discount rates. Additional information on the undiscounted QALY gains was made available to the Committee.

Table 5.3 – Scenario analysis (PAS discount on burosumab)

	Scenario description	Base case description	Incr costs (£)	Incr QALYs	ICER (£/QALY)
1	Time horizon: 70yrs	Time horizon: 93yrs	709,378	5.49	129,251
2	Time horizon: 80yrs		709,046	5.57	127,411
3	Proportion of patients female = 66.7%	Proportion of patients female = 50%	672,551	5.60	120,047
4	Maximum stopping ages (girls 16yrs, boys 17yrs)	Maximum stopping ages (girls 14yrs, boys 16yrs)	867,554	5.59	155,326
5	1 carer disutility per patient	Carer disutility excluded	708,957	6.00	118,167
6	2 carer disutility per patient		708,957	6.41	110,535
7	Burosumab average dose = 0.912 mg/kg (adjusted for observed	Burosumab average dose = 0.8 mg/kg	800,628	5.59	143,344

	data from CL301 study – 28% receive dose of 1.2 mg/kg)				
8	Burosumab average dose = 1.17 mg/kg (Matched to Walker et al. (2023))[20]		1,028,075	5.59	184,065
9	Long term health state fixed at occupancy at end of year 1	Long term health state fixed at occupancy at end of year 11 (i.e. 18yrs old)	720,466	2.67	269,524
10	Treatment waning: 30yrs	No treatment waning	708,957	4.69	151,237
11	Treatment waning: 50yrs		708,957	5.28	134,395
12	Treatment waning: 70yrs		708,957	5.52	128,497
13	Increased frequency and cost of orthopaedic interventions (cost per cycle £780.62)	Original frequency and cost of orthopaedic interventions (Cost per cycle £114.20)	NR	NR	75,075
	Combination scenarios				
14	• Proportion female =66.7% • 2 carer disutilities		672,551	6.43	104,581
15	• Proportion female =66.7% • Maximum stopping ages (girls 16yrs, boys 17yrs) • 2 carer disutilities • Long term health state fixed at occupancy at end of year 1		859,861	3.32	258,857

Incr: incremental, QALY: quality adjusted life year, ICER: incremental cost effectiveness ratio

5.4. Key strengths:

- The economic modelling matched the licensed indication.
- The submission used randomised evidence comparing burosumab with a relevant comparator.
- A wide range of sensitivity and scenario analysis was provided which helped explore and understand areas of uncertainty.

5.5. Key uncertainties:

- The model assumed treatment would commence in patients aged 7 years, matched to the mean age of patients at the start of the CL201, CL205 and CL301 studies. No patients in the studies started treatment beyond the age of 12, and so the applicability of that clinical evidence, and the resulting economic model inputs, to children starting treatment later was uncertain. The company provided supportive evidence that the different age groups would see similar response levels in terms of increased serum phosphate, but it was unclear how this would translate into changes in rickets severity. The company made the reasonable argument that the pool of older children initiating treatment would diminish if burosumab is approved and becomes more integrated into the treatment pathway.
- The model currently applies annualised transition probabilities, derived from the observed 64-week clinical study data, for each cycle from the age of 1 to 18. This did not account for the stabilisation of RSS which is apparent in longer follow up data, and instead assumed that a continued proportion of burosumab patients would move into the healed state over time. This may have overstated the benefits of burosumab.

Assuming that transition probabilities only applied in the first year led to a significant increase in the incremental cost-effectiveness ratio (ICER) (see Scenario 9).

- The long-term outcomes of patients receiving burosumab were unknown, which introduced uncertainty into the economics results. In terms of outcomes, the model assumed that patients remain in the same health state from age 18 to the end of their life. This may not account for the effect of osteomalacia in adulthood, which could lead to the deterioration of the patient's health state over time. Scenarios assuming treatment waning effects, and the decline in health state across time, led to large increased in the ICER (see Scenarios 10 to 12). Further, no retreatment with burosumab later in life was included. If additional treatment in adulthood was to take place, this could increase costs considerably, and reduce the cost-effectiveness of burosumab.
- The process of estimating utility did not involve any input from patients with XLH or their caregivers. Therefore the utilities applied in the model represent the impact of the disease through the perspective of clinical experts, rather than those with a more complete understanding of the impact of the condition on day-to-day activities. It was unclear whether these values were appropriate and a comparison against other health conditions suggested that they have been over- and underestimated for healed and severe patients respectively. An additional study conducted after the initial assessment in 2020 collected EQ-5D data from children with XLH, and generated utility values for the healed and mild states. These were numerically lower than the base case values. While the base case values sat within the 95% confidence intervals of the estimates generated from the direct elicitation exercise, those confidence intervals were wide, due to the small sample size. While a small sample size is understandable in a rare condition, it did mean the base case values could not be robustly validated.

6. Conclusion

The Committee considered the benefits of burosumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as burosumab is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted burosumab for use in NHSScotland.

7. Costs to NHS and Personal Social Services

The submitting company estimates that there will be around 14 patients eligible for treatment with burosumab each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

8. Guidelines and protocols

In 2019, a group of European specialists (in paediatrics, nephrology, orthopaedics and rheumatology) published: Clinical Practice Recommendations for the Diagnosis and Management of X-linked hypophosphataemia. The consensus statement provided recommendations for the use of standard therapy and the use of the newly introduced burosumab.[3]

In 2020, the British Paediatric and Adolescent Bone Group published clinical guidelines for burosumab in the treatment of X-linked hypophosphataemia in children and adolescents: British Paediatric and Adolescent Bone Group recommendations.[28]

In 2022, a working group of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases published a consensus statement on the evaluation, diagnosis and care of patients with X-linked hypophosphataemia.[29]

9. Additional information

9.1. Date of licensing

Burosumab was granted a conditional marketing authorisation in January 2019 and this was converted to a full marketing authorisation by the MHRA in October 2022.

9.2. Product availability date

January 2019

Table 9.1 List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
burosumab	**Starting dose: 0.8 mg/kg given every 2 weeks by subcutaneous injection.** **Maximum dose: 2.0 mg/kg (maximum dose of 90mg).**	**77,792 to 466,752** **700,128 (90mg)**

Costs for burosumab from BNF online on 29 August 2023. Costs for burosumab range from the starting dose (0.8 mg/kg) estimated for patient weight 10 kg to 70 kg and for the maximum recommended dose (90mg). Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

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This assessment is based on data submitted by the applicant company up to and including 13 October 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC assessment report.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When a medicine is available through the ultra-orphan pathway, a set of guidance notes on the operation of the patient access scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC assessment report.

Assessment report context:

No part of the assessment summary on page one may be used without the whole of the summary being quoted in full.

This assessment represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.