Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Burosumab (Crysvita)

Indication: for the treatment of X-linked hypophosphataemia (XLH) in adult and pediatric patients 6 months of age and older

Sponsor: Kyowa Kirin Canada, Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that burosumab be reimbursed for the treatment of X-linked hypophosphataemia (XLH) in adult patients only if the conditions listed in **Error! Reference source not found.** are met.

The CDEC recommendation for burosumab to be reimbursed for treatment of XLH when initiated in pediatric patients who are at least one year of age and in whom epiphyseal closure has not yet occurred, dated May 2020, continues to apply along with the associated initiation, renewal, discontinuation, prescribing, and pricing conditions.

Rationale for the Recommendation

XLH is a rare disease with notable morbidity and mortality in patients. Unmet needs that were highlighted by the patient group included medication that was accessible, affordable, easier to take, boosting energy and muscle function, reducing pain, improving health related quality of life (HRQoL) and having fewer side effects.

One phase III randomized controlled trial (CL303) in adults with XLH aged 18 to 65, inclusive, provided evidence of burosumab relative to placebo for 24 weeks, and additional data from the open-label extensions to weeks 48 and 96 were submitted as part of the sponsor's reassessment to address CDEC's concern over a lack of statistically significant results in the domains of pain, physical function, and fatigue in adults with XLH. CL303 reported that normalization of serum phosphorus, reported as proportion with serum phosphorus greater than the lower limit of normal, occurred in a majority of patients and persisted in many patients over time, although a waning in this proportion was observed at week 96. A trend towards increased healing in fractures or pseudofractures was also noted along with statistically significant odds of full healing relative to no healing at all at 24 weeks. Reductions in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, particularly stiffness scores, were reported and maintained over weeks 48 and 96. However, CDEC noted that there was a lack of HRQoL outcomes assessed in the body of evidence.

Conventional therapy, which consists of active vitamin D and oral phosphate supplements, is the only relevant comparator for burosumab at this time. To address the additional concern from CDEC's first review of burosumab that there was a lack of comparative data for adults with XLH the sponsor submitted a matched cohort study from the first year of data of a real-world disease monitoring program. The reassessment was not able to reach firm conclusions about comparative efficacy due to limitations in the real-world evidence, and no information was collected on the safety or HRQoL outcomes for burosumab relative to conventional therapy.

While acknowledging limitations in the body of evidence submitted for this reassessment, CDEC concluded that burosumab potentially met a number of patient needs and provided enough evidence to suggest a meaningful impact to patients, noting potential improvements in domains such as pain interference and stiffness, along with improved fracture healing.

Using the sponsor submitted price for burosumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for burosumab was $1,680,920 per quality-adjusted life-year (QALY) compared with standard of care (SoC). At this ICER, burosumab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adult patients with XLH. A price reduction is required for burosumab to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients 18 years of age or older.	Study CL303 enrolled adults with XLH aged 18 to 65 (inclusive).	—
2. Diagnosis of XLH supported by classic clinical features of adult XLH (such as short stature or bowed legs) and both of the following: 2.1. a confirmed *PHEX* gene variant in either the patient or a directly related family member with appropriate X-linked inheritance 2.2. Serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos assay	Study CL303 enrolled patients with a diagnosis of XLH supported by classic clinical features of adult XLH (such as short stature or bowed legs) and at least one of the following at Screening: 1. Documented PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance 2. Serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos assay	The sponsor should cover the cost of the PHEX mutation testing required to support the diagnosis of XLH.
3. Biochemical findings consistent with XLH following overnight fasting (minimum 8 hours): 3.1. Serum phosphorus less than 0.81 mmol/L 3.2. TmP/GFR of less than 2.5 mg/dL	Study CL303 enrolled patients with the following biochemical findings consistent with XLH at the second screening visit, following overnight fasting (minimum 8 hours): serum phosphorus less than 0.81 mmol/L and TmP/GFR less than 2.5 mg/dL	—
4. Estimated GFR of 60 mL/min or greater; or estimated GFR ranging from 45 mL/min to less than 60 mL/min with confirmation that the renal insufficiency is not due to nephrocalcinosis.	Study CL303 enrolled patients with an estimated GFR of 60 mL/min or greater (using the Chronic Kidney Disease Epidemiology Collaboration equation); or estimated GFR ranging from 45 mL/min to less than 60 mL/min at the second screening visit, with confirmation that the renal insufficiency was not due to nephrocalcinosis	—
5. Presence of skeletal pain that the treating physician attributes to XLH and/or osteomalacia.	Study CL303 enrolled patients with the presence of skeletal pain attributed to XLH and/or osteomalacia, as defined by a score of 4 or greater on BPI Worst Pain at the first screening visit.	The inclusion criteria for study CL303 defined pain attributes to XLH and/or osteomalacia as a BPI Worst Pain score of 4 or greater at the first screening visit. Skeletal pain which, in the opinion of the investigator, was attributed solely to causes other than XLH and/or osteomalacia — for example, back or joint pain in the presence of severe osteoarthritis by radiograph in that anatomical location — in the absence of any skeletal pain likely attributed to XLH and/or osteomalacia would not be considered for eligibility.
6. Insufficient response or refractory to conventional therapy (defined as active vitamin D and oral phosphate supplementation), defined as either:	The ongoing presence of radiographic symptoms of XLH despite conventional therapy suggests failure of therapy. The development of hyperparathyroidism or	—

Reimbursement condition	Reason	Implementation guidance
6.1. Presence of either radiographic evidence of osteomalacia, nonhealing complete fractures or nonhealing incomplete fractures after 1 year of therapy, or 6.2. the development of hyperparathyroidism or nephrocalcinosis	nephrocalcinosis are known side effects of conventional therapy.	
Renewal		
7. Patients should be reassessed on an annual basis. Treatment with burosumab can be renewed as long as the patient does not meet any of the discontinuation criteria.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and reduce the risk of unnecessary treatment.	The clinical expert noted to CDEC that therapy with burosumab is likely to be lifelong.
Discontinuation		
8. Burosumab should be discontinued if any of the following develop or progress while on treatment: hyperparathyroidism, nephrocalcinosis, evidence of fracture or pseudofracture based on radiographic assessment, or fasting hypophosphatemia	Evidence of these events suggests failure of therapy in patients.	—
Prescribing		
9. Burosumab must only be prescribed by an endocrinologist or rheumatologist with experience in the diagnosis and management of XLH.	Accurate diagnosis and management of patients with XLH is important to ensure that burosumab is prescribed to appropriate patients.	—
Pricing		
10. A reduction in price.	The ICER for burosumab is $1,680,920 per QALY when compared with SoC; a price reduction of 99.8% would be required for burosumab to achieve an ICER of $50,000 per QALY compared to SoC.	—
Feasibility of adoption		
11. The economic feasibility of adoption of burosumab must be addressed.	At the submitted price, the incremental budget impact of burosumab is expected to be greater than $40 million in years 1, 2, and 3.	—

BPI = Brief Pain Inventory; GFR = glomerular filtration rate; ICER = incremental cost-effectiveness ratio; PHEX = phosphate-regulating endopeptidase homolog, X-linked; QALY = quality-adjusted life year; SoC = standard of care; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; XLH = X-linked hypophosphatemia.

Discussion Points

- The sponsor requested a reassessment of the initial recommendation for burosumab to reimburse with conditions, where the conditions only pertained to the pediatric indication. The requested change from the sponsor was to review additional information submitted for adults with XLH, as burosumab also has a Health Canada indication for treatment of adults. A lack of comparative data for burosumab and a lack of statistically significant results in the domains of pain, physical function and fatigue were areas highlighted by CDEC in the initial review, which sponsor submitted additional information to address.
- Given the uncertainty in the clinical evidence, CDEC considered the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. Considering the rarity and severity of XLH and the limitations of alternative treatments CDEC concluded that the available evidence suggests that burosumab has the potential to reduce morbidity associated with the disease despite the limitations in the additional evidence submitted, which precluded firm conclusions on the meaningfulness of results in most domains identified by patients, and on the comparative efficacy of burosumab. The clinical expert noted that improvements in pain or QoL may take time to see if they are related to fracture healing, and the duration of study CL303 may not be sufficient to capture these results.
- During the reassessment meeting, CDEC discussed that unmet needs exist in the adult population with XLH. XLH is associated with significant morbidity; is a rare disease; current therapy only targets downstream effects of the disease mechanism and is susceptible to reduced efficacy via a feedback loop; and the majority of patients continue to have symptoms according to the clinical expert.
- During the reassessment meeting, CDEC discussed that patients who would most benefit from burosumab are adult patients with XLH who are refractory to conventional therapy. The clinical expert suggested that a trial of 1 to 2 years would be sufficient to determine whether conventional therapy would be effective in these patients. CDEC noted that the exact duration of therapy required to determine refractoriness to conventional therapy is unclear and may vary.
- The additional data submitted for the reassessment reported that the majority of patients in both treatment arms at 48 weeks and 96 weeks had midpoint serum phosphorus greater than the lower limit of normal, and there was a trend towards improved fracture healing at 24 and 48 weeks. Sustained numeric reductions in BPI Pain Interference and WOMAC Stiffness scores which surpassed the sponsor-provided Minimal Clinically Important Change (MCID) were also observed, however clinically meaningful score reductions in other quality of life domains (Worst Pain, BFI, WOMAC Physical Function) were not observed. This indicates that burosumab may meet some important patient needs such as pain interference reduction and stiffness, but the committee discussed that the evidence is not certain enough due to limitations with the MCIDs provided by the sponsor and the lack of clinically meaningful reductions in the other domains. CDEC discussed that the MCIDs provided by the sponsor were impacted by limitations in the data sources used to derive them, including the fact that CL303 was used both as a data source for the MCIDs and the data source for the pivotal trial in the submission. Therefore, there remains no external MCID in patients with XLH.
- During the initial meeting, the lack of comparative data for burosumab relative to conventional therapy was discussed by CDEC, and the sponsor submitted a matched cohort study analyzing the first year of data from a real-world disease monitoring program. Limitations in the submitted evidence rendered the results uncertain and subject to bias. Furthermore, there was no statistically significant improvement in physical function or stiffness outcomes, and no HRQoL measures or harms data was reported, leaving an important information gap.
- CDEC discussed the uncertainty in the economic analysis, specifically that in the absence of robust comparative evidence, the incremental gain in QALYs with burosumab treatment predicted in CADTH's reanalysis may still overestimate the incremental benefits relative to conventional therapies, and further price reductions may therefore be required.
- CDEC noted that burosumab is a costly treatment, and the uncertainty of the estimated budget impact of reimbursing burosumab may have implications for the feasibility of adoption, particularly if diagnosis rate increases and uptake of burosumab is higher than expected given the lack of other active treatments in this disease space.

Background

X-linked Hypophosphatemia (XLH) is a rare, chronically debilitating genetic disorder characterized by renal phosphate wasting and consequent defective bone mineralization caused by inactivating mutations in Phosphate Regulating Endopeptidase X-linked (PHEX). Patients with XLH produce excess fibroblast growth factor 23 (FGF23), leading to impaired conservation of phosphate and consequent hypophosphatemia, suppression of 1,25 dihydroxyvitamin D (1,25$[OH]_2$D) production and a resulting decrease in intestinal absorption of calcium and phosphate. XLH in children is characterized by vitamin D-resistant rickets. While adults with XLH

can display manifestations such as osteomalacia, fractures and pseudofractures, early-onset osteoarthritis and enthesopathies. These abnormalities in adults with XLH result in musculoskeletal pain and stiffness, impaired mobility and physical function, fatigue, and reduced health-related quality of life (HRQoL). Published information about the incidence and prevalence of XLH is limited. The estimated prevalence of XLH in Norway is one case per 100,000 children. The estimated prevalence of hypophosphatemic rickets in southern Denmark is 4.8 per 100,000 people (children and adults),15 and 2.03 cases per 100,000 people in Colombia. There are no known reported prevalence estimates for Canada.

In adults, primary treatment generally consists of oral phosphate and active vitamin D analogues (conventional therapy) as well as pain management and orthopedic interventions. Active vitamin D analogues are publicly funded for XLH, while phosphate supplementation is accessible as an over-the-counter product. Current treatment generally does not reverse the course of disease. Furthermore, frequent phosphate administration may produce gastrointestinal upset and secondary or tertiary hyperparathyroidism, $1,25(OH)_2D$ treatment may produce hypercalciuria and nephrocalcinosis that may potentially lead to renal failure, and patients who respond with normalization of serum phosphate and $1,25(OH)_2D$ may develop further elevated FGF23 levels which limit the efficacy of conventional treatment. Burosumab has been approved by Health Canada for the treatment of XLH in adult and pediatric patients 6 months of age and older. It is a human monoclonal antibody that inhibits the biological activity of FGF23. It is available as a sterile, preservative-free, clear to slightly opalescent, and colourless to pale brown-yellow solution in a single-use vial. The dosing regimen recommended in the product monograph is 1 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered every four weeks. Dose recalculation should be performed if there are changes in patient weight of ±10%.

Submission History

Burosumab was previously reviewed by CADTH and received a recommendation to reimburse with conditions for the treatment of pediatric patients with XLH from the CDEC on May 27, 2020; a recommendation was issued not to reimburse in adults with XLH. The original CADTH review of burosumab included 4 unique trials – CL201, CL205, CL301, and CL303.

Study CL201 was a Phase II randomized, open-label dose-finding study of 52 children between 5 and 12 years of age with open growth plates and a diagnosis of XLH, confirmed *PHEX* mutation, radiographic evidence of active bone disease, standing height less than 50^{th} percentile and fasting serum phosphate less than or equal to 0.904 mmol/L. CL205 was a Phase II single arm, open-label study in 13 children aged 1 year to less than 5 years, with confirmed *PHEX* mutation, biochemical findings associated with XLH, and radiographic evidence of rickets. CL301 was a Phase III, randomized open-label trial in 61 children aged 1 to 12 years, with radiographic evidence of rickets, *PHEX* mutation, fasting serum phosphorus less than or equal to 3.0 mg/dL (0.97 mmol/L), fasting serum creatinine below the age-adjusted upper limit of normal, serum $1,25(OH)_2D$ equal to or above 16ng/mL at screening, and who have received both oral phosphate and active vitamin D for 12 or more consecutive months if aged 3 or older, or 6 or more consecutive months if aged less than 3 years. CL303 was a Phase III, double-blind, placebo-controlled RCT in 134 adult patients aged 18 to 65 with diagnosed XLH, documented *PHEX* mutations, biochemical findings consistent with XLH, presence of skeletal pain attributed to XLH or osteiomalacia, estimated glomerular filtration rate (GFR) 60mL/min or greater, and on a stable regimen of pain control medications, if taking them.

In the previous submission CDEC recommended to reimburse burosumab if initiated in pediatric patients but identified gaps in evidence the reimbursement request in adults with XLH, and hence CDEC recommended not to reimburse burosumab if initiated in adult patients. CDEC identified concerns over a lack of statistically significant results in the domains of pain, physical function and fatigue in adults with XLH, as well as a lack of comparative data for burosumab versus conventional therapy. This reassessment is based on additional data submitted by the sponsor to address these concerns, as the adult population is included within the indication approved by Health Canada.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 randomized, double-blind placebo-controlled trial with an open-label single arm extension in adults with XLH; 1 long-term extension study; and 1 matched cohort study analyzing the first year of real-world evidence from an ongoing disease monitoring program

- patients' perspectives gathered by 1 patient group, the Canadian XLH Network
- input from public drug plans that participate in the CADTH review process
- One clinical specialist with expertise diagnosing and treating adult patients with XLH
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for reassessment

Stakeholder Perspectives

Patient Input

Input was submitted for this review by the Canadian XLH Network, a national, not-for-profit, patient support organization for people living and dealing with XLH. Information for this input was gathered through an online survey of XLH adult patients, family and caregivers from December 2 to December 15, 2023.

Survey respondents indicated that symptoms of XLH during adulthood differed from childhood symptoms. When asked about adult symptoms, 44% of patients reported severe pain, 28% loss of mobility, 21% lack of energy, 21% had an increase in dental issues, and 26% had developed arthritis and/or spinal stenosis, all of which were reported to significantly impact patients' quality of life as well as their social and psychological wellbeing.

Survey respondents indicated that with conventional treatment (a combination of phosphate and calcitriol) patients need to take large doses of phosphate up to 5 times daily and calcitriol 1 to 2 times daily, which addresses the issue of low phosphate but does not address pain and other serious symptoms of XLH. In addition, conventional treatment has serious side effects, such as nephrocalcinosis, kidney disease, calcium deposits, and parathyroid issues, all while allowing XLH to continue progressing. Furthermore, phosphate is very expensive and hard to access due to supply chain issues.

Respondents indicated that there is a need for treatment options that are accessible, affordable, and easier to take and can boost energy levels and muscle function, reduce pain, and improve bone health and overall quality of life, with fewer side effects.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical expert noted that the goals of treatment in adults are to reduce osteomalacia and pseudofractures in order to alleviate generalized bone pain, enhance mobility which may be reduced, and cure any nonunion fractures. Unmet needs pertained to the fact that current treatment reduces downstream effects of the elevated FGF23 levels. However, the treatment, by while attempting to normalize serum phosphate and $1,25(OH)_2D$, may further elevate FGF23 levels to cause a feedback loop which limits the efficacy of conventional treatment. The clinical expert also noted that there is a side effect burden to conventional therapy, including gastrointestinal upset due to oral phosphate, and hypercalcuria and nephrocalcinosis due to $1,25(OH)_2D$ treatment, which can reduce kidney function and cause secondary hyperparathyroidism. In addition, the clinical expert stated that the majority (> 70%) of patients continue to have symptoms of pain, mobility issues or complications despite treatment. Furthermore, since active vitamin D may need to be administered twice daily and oral phosphate is usually administered several times per day, adherence may not be optimal.

Per the clinical expert, burosumab would represent a shift in the current treatment paradigm as it addresses the underlying disease at an upstream rather than a downstream level. They noted that treatment with burosumab is likely to be lifelong as the cause of the disease is a genetic mutation which results in consequences that persist throughout life.

Per the clinical expert, symptomatic patients with bone pain due to bone disease (i.e., due to osteomalacia, pseudofractures and nonunion fractures) are best suited for treatment. However, they also noted there may be benefit in adults with limited symptomatology to increase activity levels and a sense of well-being.

In the clinical expert's practice, they would consider reduction in bone pain, reduction in fractures and healing of fractures to be clinically meaningful responses to therapy. Laboratory evidence of normalization of serum phosphate and biomarkers of bone metabolism (e.g., alkaline phosphatase) and the absence of elevations in serum creatinine or parathyroid hormone (PTH) as well as absence of development or acceleration of nephrocalcinosis would also be considered clinically meaningful responses.

The clinical expert noted that patients who are experiencing a sustained decline in serum phosphate despite adherence to therapy (suggesting that burosumab treatment is not working), or who develop a severe allergic reaction to burosumab, should discontinue therapy. Therapy should be continued if initiated during childhood as long as the patient does not meet any of the discontinuation criteria, since the consequences of elevated FGF23 can also be seen in adults. Specialist attention would likely be required to diagnose, treat and monitor patients receiving burosumab, i.e., either an endocrinologist or rheumatologist with knowledge of the disorder.

Clinician Group Input

No input was received by clinician groups by the deadline of the call for input.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for burosumab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation Issues	Response
Considerations for initiation of therapy	
CADTH's initial recommended initiation criteria for pediatrics requires radiographic evidence of rickets with a RSS total score of two or greater. Given that rickets is predominately a childhood condition, is the RSS an appropriate tool to evaluate XLH rickets in adults? • If so, should the same minimum RSS of two or greater be required to be eligible for treatment? • If not, is there an alternative score that can be used to measure osteomalacia in adults?	The clinical expert noted to CDEC that XLH in children presents with rickets and osteomalacia and in adults the manifestation is osteomalacia alone as the epiphyseal plates are closed. The most common measurement of osteomalacia is a qualitative description based on X-Ray evidence; the clinical expert was not aware of a standardized scoring system for osteomalacia.
The inclusion criteria of the pivotal trial, CL303, were as follows: • Aged 18-65 years	CDEC agreed with the clinical expert that the study inclusion criteria identify patients with symptomatic XLH and are applicable to patients in the expert's context.

Implementation Issues	Response
• A diagnosis of XLH supported by a confirmed *PHEX* mutation (self or family member consistent with X-linked inheritance) and/or prespecified clinical findings and laboratory features • Serum phosphate below the LLN, 2.5 mg/dL (0.81 mmol/L) • TmP/GFR below 2.5 mg/dL • BPI worst pain score of ≥4 Should any of the above inclusion criteria in CL303 be used as reimbursement criteria for patients initiating therapy in adulthood?	CDEC however recommended that Diagnosis of XLH be supported by classic clinical features of adult XLH (such as short stature or bowed legs) and both a confirmed *PHEX* gene variant in either the patient or a directly related family member with appropriate X-linked inheritance and Serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos assay, rather either a confirmed PHEX gene variant or Serum intact FGF23 (iFGF23) level > 30 pg/mL CDEC agreed with the clinical expert that treatment can also be initiated in patients who are older than 65 years of age, however it would depend on other factors such as their state of health and symptoms.
For patients who either have an insufficient response or are refractory to conventional therapy, what duration of a trial to conventional therapy should be required?	The clinical expert noted to CDEC that they would suggest a trial of 1-2 years with conventional therapy; the ongoing presence of symptoms, the presence of nonhealing complete fractures or nonhealing incomplete fractures after this period, or the development of manifestations such as secondary hyperparathyroidism or kidney manifestations would be the signal to change. The expert noted that it is difficult to normalize serum phosphorus with conventional therapy and so the development of secondary effects would be a more reasonable measure of treatment failure than serum phosphorus. They noted that if the development of parathyroid or kidney manifestations occurred before 2 years, it would be the signal to stop. There is no clear consensus on the duration of a trial with conventional therapy prior to initiating treatment with burosumab.
For patients who are undergoing treatment with burosumab for a time-limited period to treat pseudofractures or osteomalacia-related fractures, should they be eligible for re-treatment if they sustain an additional fracture post-treatment?	CDEC agreed with the clinical expert noting that burosumab would likely be a lifelong therapy as the biochemical and clinical manifestations of XLH are lifelong. If a patient stopped burosumab treatment and then developed a new fracture, they should restart treatment.
The sponsor requested reimbursement for patients with the following indications: […] • Persistent bone and/or joint pain due to XLH, and/or • Osteomalacia that limits daily activities, and/or • Pseudofractures or osteomalacia-related fractures […] Is there evidence that patients with recurrent dental complications of XLH in the absence of the above manifestations can be considered for a trial with burosumab?	The clinical expert noted to CDEC that dental issues are not the most specific manifestations of XLH, particularly because as patients age there could be a number of other causes contributing to dental abscesses and it is not very specific on its own.
Considerations for continuation or renewal of therapy	
The current initiation criteria for coverage with burosumab do not contain any specific details about patients with nephrocalcinosis, however the current renewal criteria for burosumab state that coverage may be renewed in patients already initiated unless any of the following occur: 1. Hyperparathyroidism, or	The clinical expert noted to CDEC that once nephrocalcinosis occurs, irrespective of the cause, it is unlikely to disappear, and the goals of therapy are to prevent its progression to the greatest extent possible. Nephrocalcinosis was not reported as a common adverse event during the burosumab clinical trials and there is no information in the trial on whether patients with reported nephrocalcinosis already had it before starting burosumab or not. Patients with nephrocalcinosis at the time of

Implementation Issues	Response
2. Nephrocalcinosis, or 3. Evidence of fracture or pseudofracture based on radiographic assessment. If a patient with nephrocalcinosis were to initiate burosumab and, upon renewal, still has this condition, they would not be eligible for renewal of coverage. Is it reasonable to infer that they are not responding to burosumab if they still have nephrocalcinosis?	initiation of burosumab therefore are likely to still have nephrocalcinosis and should be eligible for renewal with burosumab.
Considerations for discontinuation of therapy	
As per the sponsor's request, the proposed initiation criteria are follows: • Persistent bone and/or joint pain due to XLH, and/or • Osteomalacia that limits daily activities, and/or • Pseudofractures or osteomalacia-related fractures If the main indication of treatment is to reduce pain and improve mobility, should a time-limited trial of burosumab be considered (i.e., one year)?	The clinical expert noted to CDEC that pain and mobility are more subjective measures, evidence of osteomalacia and/or pseudofracture would be more compelling and these contribute to pain and mobility. They noted that burosumab doesn't seem to impact enthesopathy or osteoarthritis outcomes, which can also cause pain and mobility issues. CDEC recommended that burosumab Diagnosis of XLH supported by classic clinical features of adult XLH and with both confirmed *PHEX* gene variant in either the patient or a directly related family member with appropriate X-linked inheritance and Serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos assay. In addition, in order to be eligible, patients have to have Biochemical findings consistent with XLH, estimated GFR of 60 mL/min or greater; or estimated GFR ranging from 45 mL/min to less than 60 mL/min with confirmation that the renal insufficiency is not due to nephrocalcinosis, and presence of skeletal pain that the treating physician attributes to XLH and/or osteomalacia The clinical expert would not consider burosumab a time-limited therapy, as XLH is a lifelong disease it requires a lifelong therapy.
If the main indication of treatment is for pseudofractures or osteomalacia-related fractures, what is an appropriate duration of trial of burosumab to assess benefit?	The clinical expert noted to CDEC that an initial 1-to-2-year trial would be needed, then an annual renewal would be reasonable improvement in biochemical markers and osteomalacia should be observable. CDEC recommended that patients should be reassessed on an annual basis, and hence the initial authorization would be for 1 year.
CADTH's initial recommended discontinuation criteria for burosumab in adults is the following: *In adolescent or adult patients who initiated burosumab based on the aforementioned criteria for pediatric patients, burosumab should be discontinued if any of the following occur: hyperparathyroidism, nephrocalcinosis, or evidence of fracture or pseudofracture based on radiographic assessment.* Should burosumab be continued in adolescent and adult patients who initiated it as pediatric patients?	CDEC agreed with the clinical expert that burosumab should be continued in adolescent and adult patients who initiated it as pediatric patients unless they meet any of the discontinuation criteria.
Care provision issues	
Are there side effects with long-term continuous treatment with burosumab that should be monitored for?	The clinical expert noted that important adverse events would be allergic reactions or injection site reactions, as well as ongoing monitoring for lack of efficacy. CDEC also noted that study CL303 reported higher rates of certain TEAE (e.g., tooth abscess and vitamin D deficiency)

BPI = Brief Pain Inventory; LLN = lower limit of normal; RRS = Rickets Severity Score; TEAE = treatment-emergent adverse event; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; XLH = X-linked hypophosphatemia.

Clinical Evidence

Systematic Review

Description of Studies

The major focus for the reassessment of this indication was additional data analysis results for the 48- and 96-week mark of the CL303 clinical trial, as well as an *ad hoc* week 48 analysis of the placebo-emergent (placebo treatment during the first 24 weeks, switching to burosumab after 24 weeks) arm. CL303, which was included in the original submission, was a Phase 3, double-blind, placebo-controlled randomized controlled trial consisting of a 24-week placebo-controlled period and 2 open-label extensions providing 96 weeks total follow-up. Patients in this study had to be aged 18 years to 65 years, inclusive, with a diagnosis of XLH supported by classic clinical features of adult XLH (such as short stature or bowed legs) and either a documented PHEX mutation (in either the patient or in a directly related family member with appropriate X-linked inheritance) or serum intact FGF23 level > 30 pg/mL by Kainos assay; biochemical findings consistent with XLH, namely serum phosphorus < 0.81 mmol/L and ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (GFR) of < 2.5 mg/dL; estimated GFR ≥60 mL/min (using the Chronic Kidney Disease Epidemiology Collaboration equation); or estimated GFR of 45 mL/min to < 60 mL/min at the second screening visit, with confirmation that the renal insufficiency was not due to nephrocalcinosis; as well as the presence of skeletal pain attributed to XLH/osteomalacia based on a Brief Pain Inventory (BPI) worst pain score ≥4 at the first screening visit.

The proportion of patients attaining serum phosphorus levels above the lower limit of normal (LLN [0.81 mmol/L]) at the midpoint of the dosing cycle from baseline to week 24 was the primary outcome of the study. Key secondary endpoints were also measured at 24 weeks and included change in the following patient-reported outcome (PRO) measures: BPI Worst Pain score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) stiffness and WOMAC physical function scores. Other secondary endpoints included domains of the BPI, WOMAC, and Brief Fatigue Inventory (BFI) measured at weeks 24, 48 and 96. The WOMAC is a self-administered questionnaire assessing pain, stiffness, and physical functioning in patients with hip and knee osteoarthritis, comprising pain, physical function and stiffness domains; a higher score indicates worse pain, stiffness, and functional limitations. The BPI is a self-reported questionnaire designed to provide information about pain intensity (the sensory dimension) and the degree to which pain interferes with daily living (the reactive dimension); a high score represents a high pain intensity or pain interference. The BFI is a self-reported questionnaire to assess the severity of fatigue and the impact of fatigue on daily functioning, measuring fatigue and the interference of fatigue on daily life; the items are measured on a 0 to 10 numeric rating scale and a score of 7 to 10 is considered severe fatigue.

The proportion of patients achieving serum phosphorus levels over the LLN at the end of their dosing cycle (i.e., 4 weeks after dosing) was also a secondary endpoint measured at week 48, as were measures of bone metabolism (bone-specific alkaline phosphatase [BALP]), $1,25(OH)_2D$, and phosphorus homeostasis (ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate [TmP/GFR] and tubular reabsorption of phosphate [TRP]), measured at weeks 24, 48 and 96. Exploratory endpoints were active pseudofractures and/or fractures, as well as the 6-metre walk test (6MWT), a supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period. Both were measured at weeks 24 and 48 (neither exploratory outcome was measured at week 96).

Baseline characteristics were generally balanced between the two treatment arms. In terms of medical history, a numerically higher proportion of patients in the burosumab arm had osteoarthritis (69.1% versus 57.6% in the placebo arm). A numerically higher proportion of patients in the burosumab arm were classified as having a BPI Average Pain score > 6.0 (32.4% in the burosumab arm and 25.6% in the placebo arm); similarly, a numerically higher proportion of patients in the burosumab arm were classified as having a BPI Worst Pain score > 6.0 (77.9% in the burosumab arm and 65.2% in the placebo arm). A numerically higher proportion of patients in the burosumab arm had nephrocalcinosis than the placebo arm (16.2% versus 7.6%, respectively). The majority of patients in burosumab and placebo arms (86.8% and 93.9%, respectively) had received both vitamin D analogs and phosphate prior to the trial. There were no notable imbalances in baseline laboratory characteristics. A higher proportion of patients in the placebo arm had active pseudofractures at baseline (51.5%) than patients in the burosumab arm (42.6%). The majority of patients in both arms had had previous orthopedic surgery (66.2% in the burosumab arm, 71.2% in the placebo arm), or were taking non-opioid pain medications at baseline (65.2% in the placebo arm and 69.1% in the burosumab arm).

Efficacy Results

Proportion of Patients with Serum Phosphorus > LLN

Following crossover to burosumab after week 24, the additional data from the reassessment reported that the proportion of patients in the placebo-emergent arm with midpoint serum phosphorus > LLN was 89.4% (95% confidence interval [CI]: 79.7 to 94.8%) at week 48 and 68.2% (95% CI: 56.2 to 78.2%) at week 96. The proportion of patients > LLN in the burosumab-emergent arm (burosumab treatment during the first 24 weeks with continued burosumab after 24 weeks) was 83.8% (95% CI: 73.3 to 90.7%) at week 48 and 82.4% (95% CI: 71.6 to 89.6%) at week 96. There was no information on the patients with endpoint serum phosphorus > LLN for weeks 48 and 96.

Brief Pain Inventory

Additional information submitted for the BPI Worst Pain scores reported that at week 48, the least squares (LS) mean change from baseline in the placebo-emergent arm was −1.53 (95% CI: −1.98 to −1.09) and burosumab-emergent arm was −1.09 (95% CI: −1.51 to −0.66). At week 96, the LS mean changes from baseline in the placebo-emergent arm was −0.99 (95% CI: −1.51 to −0.47) and burosumab-emergent arm was −1.48 (95% CI: −2.07 to −0.90).

BPI Pain Interference results at week 48 reported a LS mean change from baseline of −1.27 (95% CI: −1.77 to −0.78) in the placebo-emergent arm and −1.04 (95% CI: −1.51 to −0.56) in the burosumab-emergent arm. At week 96, the LS mean change from baseline was −1.08 (95% CI: −1.59 to −0.57) in the placebo-emergent arm and −1.43 (95% CI: −1.89 to −0.97) in the burosumab-emergent arm.

BPI Pain Severity results reported that at week 48, the LS mean change from baseline in the two study arms was −1.20 (95% CI: −1.58 to −0.81) in the placebo-emergent group and −0.85 (95% CI: −1.16 to −0.54) in the burosumab-emergent group. At week 96, the LS mean change from baseline was −1.18 (95% CI: −1.57 to −0.80) in the placebo-emergent arm and −1.42 (95% CI: −1.87 to −0.97) in the burosumab-emergent arm.

Western Ontario and McMaster Universities Osteoarthritis Index

For WOMAC Physical Function, at week 48, the LS mean change from baseline was –6.35 (95% CI: –11.94 to –0.76) in the placebo-emergent arm and –7.76 (95% CI: –11.97 to –3.55) in the burosumab-emergent arm. At week 96, the LS mean change from baseline was –8.41 (95% CI: –13.80 to –3.01) in the placebo-emergent arm and –9.02 (95% CI: –13.47 to –4.57) in the burosumab-emergent arm.

WOMAC Stiffness scores reported that at week 48, the LS mean change from baseline was –15.29 (95% CI: –22.23 to –8.35) for the placebo-emergent arm and –16.03 (95% CI: –22.53 to –9.53) in the burosumab-emergent arm. At week 96, the LS mean change from baseline was –17.67 (95% CI: –24.99 to –10.34) in the placebo-emergent arm and –15.32 (95% CI: –22.33 to –8.31) in the burosumab-emergent arm.

WOMAC Pain scores were not analyzed, but a trend towards numerically increasing reductions was reported between weeks 48 and 96, for both placebo-emergent and burosumab-emergent treatment arms.

6MWT

At week 48, the mean total distance walked at baseline was 367.28 (SD = 104.22) in the placebo-emergent arm and 365.66 (SD = 125.44) in the burosumab-emergent arm. The LS mean change from baseline in total distance walked was –5.71 (95% CI: –21.70 to 10.28) in the placebo-emergent arm and 5.92 (95% CI: –15.00 to 26.84) in the burosumab-emergent arm. This outcome was not measured at week 96.

Brief Fatigue Inventory

At week 48, the LS mean change from baseline in BFI Worst Fatigue was –1.23 (95% CI: –1.84 to –0.62) in the placebo-emergent arm and –1.01 (95% CI: –1.57 to –0.45) in the burosumab-emergent arm. At week 96, the LS mean change from baseline was –0.82 (95% CI: –1.53 to –0.11) in the placebo-emergent arm and –0.75 (95% CI: –1.35 to –0.26) in the burosumab-emergent arm.

At week 48, the LS mean change from baseline in BFI Global Fatigue was –0.73 (95% CI: –1.34 to –0.12) in the placebo-emergent arm and –0.46 (95% CI: –1.01 to 0.09) in the burosumab-emergent arm. At week 96, the LS mean change from baseline was –0.86 (95% CI: –1.43 to –0.29) in the placebo-emergent arm and –0.80 (95% CI: –1.36 to –0.25) in the burosumab-emergent arm.

Fractures and Pseudofractures

The reassessment submission's additional 24-week analyses reported a higher probability of a fully healed fracture at 24 weeks in the burosumab arm (0.458 vs. 0.048 in the placebo arm), (OR = 16.76 [95% CI: 4.93 to 56.95]).

At 48 weeks, 46.2% of patients in the placebo arm and 57.1% of patients in the burosumab arm reported healed active fractures. In addition, 33.3% of patients in the placebo-emergent arm and 64.7% of patients in the burosumab-emergent arm reported healed pseudofractures. The probability of a fully-healed fracture was 0.725 (95% CI: 0.516 to 0.933) in the burosumab-emergent arm and 0.386 (95% CI: 0.718 to 0.594) in the placebo-emergent arm. Fracture outcomes were not measured at 96 weeks.

Key Serum Biomarkers

At week 48, the LS mean change from baseline for the levels of serum $1,25(OH)_2D$ was 10.50 (95% CI: 5.76 to 15.24) in the placebo-emergent arm and 7.24 (95% CI: 2.44 to 12.04) in the burosumab-emergent arm. At week 96, the serum $1,25(OH)_2D$ was 3.43 (95% CI: –1.17 to 8.03) in the placebo-emergent arm and 1.95 (95% CI: –2.66 to 6.57) in the burosumab-emergent arm.

At week 48, the LS mean change from baseline in TmP/GFR in the placebo-emergent arm was 0.55 (95% CI: 0.38 to 0.72) and was 0.48 (95% CI: 0.30 to 0.65) in the burosumab-emergent arm. At week 96, the LS mean change was 0.29 (95% CI: 0.12 to 0.46) in the placebo-emergent arm and 0.46 (95% CI: 0.29 to 0.62) in the burosumab-emergent arm.

At week 48, the LS mean change from baseline in TRP was 0.02 (95% CI: 0.00 to 0.05) for the placebo-emergent arm and 0.03 (95% CI: 0.02 to 0.05) in the burosumab-emergent arm. At week 96, LS mean changes from baseline in the placebo-emergent group was –0.01 (95% CI: –0.04 to 0.02), while the burosumab-emergent group was 0.03 (95% CI: 0.01 to 0.05).

At week 48, the LS mean change from baseline in BALP in the placebo-emergent arm was 6.69 (95% CI: 2.91 to 10.47) and in the burosumab-emergent arm was 0.23 (95% CI: –3.36 to 3.81). At week 96, the LS mean change in the placebo-emergent arm was –2.49 (95% CI: –6.19 to 1.21) and –2.76 (95% CI: –5.98 to 0.45) in the burosumab-emergent arm.

Harms Results

Overall, 97% in the placebo-emergent arm and 100% in the burosumab-emergent arm experienced a treatment-emergent adverse event (TEAE). There were differences between the proportions of patients experiencing some TEAEs between the burosumab-emergent arm during the trial and the placebo-emergent arm after initiating burosumab. Specifically, there were differences in the proportion of patients reporting tooth abscesses (28% and 8%, respectively), vitamin D deficiency (22% and 11%, respectively), injection site reactions (12% and 25%, respectively), diarrhea (19% and 8%, respectively), upper respiratory tract infection (18% and 3%, respectively), nausea and dizziness (both 16% and 8% in each arm, respectively), depression (13% and 5%, respectively), hypoesthesia (10% and 5%, respectively), migraine (10% and 3%, respectively), oropharyngeal pain (6% and 12%, respectively), injection site pruritis (4% and 12%, respectively), and ectopic mineralization (0% and 11%, respectively).

During the placebo-controlled period, a serious adverse event (SAE) was reported in 1 patient in the placebo-emergent arm and 2 patients in the burosumab-emergent arm. In the placebo-emergent arm during burosumab treatment, 10 patients overall reported SAEs. The burosumab-emergent arm reported SAEs in 12 patients during the whole trial. There were no withdrawals due to adverse events (AEs) and 1 death due to a traffic accident in the burosumab-emergent arm (judged not related to treatment).

AEs of special interest included injection site reactions, hypersensitivity, hyperphosphatemia, ectopic mineralization, and restless leg syndrome. A total of 16 patients (24%) in the placebo-emergent arm reported injection-site reactions after initiating burosumab and 8 patients (12%) reported injection site reactions prior to initiating burosumab. In addition, 7 patients (11%) in the placebo-emergent arm experienced ectopic mineralization, which was not reported in any of the other treatment arms.

Noting the higher proportions of patients in the burosumab-emergent arm experiencing treatment-emergent adverse events (TEAEs) and serious TEAEs, the submission included an exposure-adjusted analysis reporting incidence rates in each arm, which reported generally similar incidence rates in the placebo-emergent and burosumab-emergent arms.

Long-Term Extension Studies

Description of Studies

Study BUR02 was an open-label, Phase 3 study evaluating the long-term efficacy and safety of burosumab in adult patients with XLH. It was undertaken using patient populations who had completed the CL303 (a Phase 3 randomized controlled trial that evaluated measures of phosphate metabolism, PROs and fractures and/or pseudofractures in adults with XLH) or CL304 (a Phase 3 single-arm study that evaluated measures of osteomalacia in patients with XLH who received burosumab treatment, not appraised in the current submission) studies. Patients completing CL303 were eligible to transition to BUR02, however there was an interval between CL303 and BUR02 (mean 9 months; range 6–16 months) where interim burosumab treatment was provided via an early access program only to the patients for whom the drug supply was accessible.

Efficacy Results

Serum phosphate above the LLN

At the baseline of BUR02, 34.3% of patients had serum phosphate above the LLN. The proportion increased to 55.9% at Week 12 and remained mostly within a range between 55% and 75% in subsequent visits. At the end of the study, 66.7% of the patients had serum phosphate above the LLN.

Key serum biomarkers

At CL303 baseline, mean TmP/GFR was 0.55 mmol/L (standard deviation [SD] = –0.15) and increased to 0.70 mmol/L (SD = 0.26) at week 12a and sustained through both studies. At the final analysis, the mean (SD) TmP/GFR was 0.62 mmol/L (SD = 0.22) and it increased to 0.69 mmol/L (SD = 0.14) at week 48b and these levels were sustained over time.

At the interim analysis, mean (SD) serum $1,25(OH)_2D$ was 79.95 pmol/L (SD = 29.77) at CL303 baseline, 98.56 pmol/L (SD = 30.27) at week 48a, and 83.36 pmol/L (SD = 32.97) at week 72a. At the baseline of BUR02, mean (SD) serum $1,25(OH)_2D$ was 78.43 pmol/L (SD = 41.49), and increased to 92.85 pmol/L (SD = 36.06) at week 12b, remaining consistent throughout the week 48b of the BUR02 study.

According to the final analysis, at baseline, the mean (SD) serum concentration of $1,25(OH)_2D$ was 32.67 pg/mL (SD = 16.35). At Week 12, the $1,25(OH)_2D$ concentration increased to 39.86 (SD = 15.57) pg/mL. At Weeks 24, 48, 72, and 96, the mean (SD) serum $1,25(OH)_2D$ levels were 36.34 pg/mL (SD = 9.80), 37.04 (SD = 7.83), 38.16 pg/mL (SD = 11.30), and 41.01 pg/mL (SD = 12.80), respectively. At the end of the study, the mean (SD) serum $1,25(OH)_2D$ was 38.53 pg/mL (SD = 12.70).

Patient Reported Outcomes

Based on the interim analyses in CL303, the least square mean (standard error [SE]) of WOMAC Stiffness scores was –14.77 (SE = 4.03) at week 36a and this reduction was sustained at all subsequent timepoints in the two studies. Similar results were reported for the WOMAC physical function score.

In the final analysis BUR02, the mean (SD) Stiffness score was 55.15 (18.75) at baseline, and the mean (SD) change was –3.13 (17.68) at Week 12. The mean stiffness scores were maintained lower than baseline throughout subsequent visits. The mean (SD) changes in stiffness score from baseline to Weeks 24, 48, and 96 were –9.19 (SD = 22.89), –8.62 (SD = 18.63), and –9.09 (SD = 20.48), respectively. At the end of the BUR02 study, the mean score decreased by –14.52 (22.61). Similar decreases were observed for the WOMAC pain score and physical function score.

Based on the interim analyses in CL303, the LS mean change from baseline in the BPI average Worst Pain scores at Week 12a was −0.88 (SE = 0.281) and decreased from baseline at all subsequent timepoints in the two studies except for week 24a. The BPI Pain

Interference scores had also decreased from baseline with a LS mean change from baseline (CfB) of −1.22 (SE = 0.309) at week 12a and at all subsequent timepoints in both studies except week 24a.

Similarly, according to the final analysis from BUR02, the mean (SD) BPI Worst Pain score was 5.78 (SD = 1.725) at baseline. The mean changes in BPI Worst Pain score from baseline to Week 12 was −0.51 (SD = 1.698), and these levels were maintained lower than baseline at weeks 24, 36, 48, 72, and 96.

The mean BPI Pain Severity score was 4.52 (SD = 1.657) at baseline (N = 32), and mean change in BPI Worst Pain score from baseline was −0.40 (SD = 1.416) at week 12 (N = 12). These values were maintained throughout subsequent visits. Similar decreases were observed for the BPI Pain Interference score.

Based on the interim analyses, the LS mean of the BPI average Worst Fatigue scores decreased from baseline results were consistent at all subsequent timepoints. Similar trends were observed for the BFI Global Fatigue score and Fatigue Interference score. The BFI Fatigue Severity scores had decreased from baseline with an LS mean of −1.45 (SE = 0.45) at week 12a and at all timepoints through to the end of BUR02.

According to the final analysis, at baseline of the BUR02 study, the mean BFI Worst Fatigue score was 5.91 (SD = 1.75). The mean change in Worst Fatigue score from baseline to weeks 24, 48, 72, and 96 were −0.49 (SD = 1.78), −0.46 (SD = 2.00), −0.34 (SD = 2.24), and −0.64 (SD = 1.73), respectively. Similar trends were observed for BFI Global Fatigue score and Fatigue Interference score.

6MWT

At the interim analysis, the 6MWT actual distance walked increased from CL303 baseline at Week 24a to Week 48b. At the final analysis, at the baseline of BUR02, the mean actual distance walked was 393.3 (SD = 93.25) m. After BUR02 entry and continuation with burosumab treatment, the mean changes in actual walking distance increased from baseline to week 12, and all subsequent visits.

Harms Results

Safety data were not evaluated as part of the interim analysis. At the final analysis, all patients had received all scheduled doses and no patients had skipped doses. Almost all patients (n = 34) experienced ≥1 TEAE but most events were mild to moderate in severity. Among the patients who experienced a TEAE, the most common TEAEs were vitamin D deficiency (55.9%), arthralgia (38.2%), and hypophosphatemia (26.5%).

Six patients experienced SAEs (17.1%) and these events occurred in single patients from each subgroup. No patients experienced related treatment-emergent SAEs. No deaths or TEAEs leading to death were reported during this study. No patients had a TEAE that led to withdrawal of study drug or study discontinuation. There was no notable difference in the overall incidence of AEs between the two subgroups.

Critical Appraisal

Internal Validity

The open-label designs of the BUR02 study could bias the magnitude of the efficacy of subjective PRO outcomes due to unblinded exposure to the study medication during the treatment period. In addition, the absence of control arms in both studies and the lack of data beyond week 96 in the study make interpretation of the long term sustainability of treatment effect challenging.

The interim analysis showed that the clinical effect of burosumab decreased when treatment was interrupted, and returned after patients resumed the medication but the analysis based on the doses received by the patients was not performed and it cannot be confirmed whether those who received one dose versus six doses of burosumab would have different outcomes.

Furthermore, treatment history and concomitant medications during the gap between the pivotal studies and BUR02 were not assessed, limiting the ability to interpret the outcomes efficiently.

External Validity

As the BUR02 study consisted of patients who took part in the parent studies (CL303, CL304), it is reasonable to expect that the same strengths and limitations related to generalizability apply to the extension studies.

The patient population of those studies may not be reflective of the wider, more heterogeneous clinical population in terms of demographic and clinical characteristics; therefore, the results presented may differ from those observed in a real-world clinical setting. The study population was not reflective of the Canadian population and therefore the patients enrolled may not reflect the gender, racial or ethnic diversity which may reduce the generalizability of results.

Indirect Comparisons

No indirect comparisons were submitted as part of this review.

Studies Addressing Gaps in the Evidence from the Systematic Review

Description of Studies

The Disease Monitoring Program (DMP) is a 10-year cohort study intended to enrol at least 500 adult and pediatric patients with XLH at up to 39 sites in the United States, Canada, and Latin America. Patients receiving burosumab in a real-world setting (i.e., outside of clinical trials), those enrolled in the DMP after receiving burosumab in a clinical trial setting, and those who are not receiving burosumab at all (i.e., receiving conventional therapy or no treatment) were included. An analysis of the Year 1 data was submitted, consisting of data collected from two matched patient cohorts: patients who are reported to be receiving conventional therapy at baseline (DMP start date: July 16, 2018) and who never received burosumab during the DMP; and patients who reported receiving burosumab in a real-world setting and who initiated burosumab at any point after DMP initiation. Patients provided information on demographics, family history, diagnostic history, medical and surgical history, growth history, disease-specific clinical symptoms and progression, concomitant medications and therapies, and disability.

Outcomes

The outcomes of interest were serum phosphate levels, WOMAC Pain, WOMAC Stiffness and WOMAC Physical Function scores at the Year 1 mark. Information on outcomes was collected at the baseline visit and again at the approximate Year 1 visit.

Statistical Analysis

The two patient cohorts were balanced on baseline characteristics using propensity score (PS) matching algorithms including the following: demographics (age, race, gender), clinical characteristics (weight, height, body mass index [BMI], serum phosphate, WOMAC Pain score, WOMAC Stiffness score, WOMAC Physical Function score), disease/medical characteristics (PHEX mutation positivity, age at XLH diagnosis, number of historical fractures, osteoarthritis, enthesopathy/bone spurs/osteophytes).

Mean changes to outcome variables between the baseline visit and the Year 1 visit were calculated for the cohorts; changes in outcomes were only calculated for those patients who had a baseline and Year 1 measure for that outcome. For continuous baseline variables, the F-test was performed to check for equality of variance between the 2 cohorts, and equal or unequal variance Student's T-test was used. For categorical baseline variables a Chi-Square test was performed with a p-value of ≤ 0.05 being considered statistically significant.

Efficacy Results

The matching procedure balanced cohorts with respect to race, weight at baseline, height at baseline, WOMAC pain and WOMAC stiffness scores. A total of 44% of patients in the burosumab cohort reported receiving conventional therapy at baseline, and 56% reported receiving no treatment. All patients in the conventional therapy cohort reported receiving conventional therapy. There was a mean delay of 245.8 (SD = 275.2) days in initiating burosumab in the burosumab cohort, and the Year 1 visit for patients occurred an average of 408.8 (SD = 94.0) days after the baseline visit in the burosumab cohort and 431.3 (SD = 89.3) days in the conventional therapy cohort.

The proportion of patients in the burosumab cohort with serum phosphorus > LLN was 20.0% at baseline and 58.3% at the Year 1 visit; this attained statistical significance relative to the conventional therapy cohort (28.6% of patients had serum phosphorus > LLN at Year 1; *P* value = 0.0013). There was no significant difference between the two cohorts in terms of the change in WOMAC Physical Function, WOMAC Pain or WOMAC Stiffness scores at the Year 1 visit.

Harms Results

Information on harms was not provided for this study.

Critical Appraisal

The design of the study is subject to some notable limitations due to missing key information. It is unclear when initiation of burosumab occurred in the burosumab cohort whereas the analysis appeared to consider the time between baseline and burosumab initiation as time spent on burosumab treatment. The treatment patterns of the cohort after baseline but prior to burosumab initiation are also not known. The dosing of all therapies during the study, conventional or burosumab, is largely unknown. While transparently discussed in the submission, this remains an important consideration as potential variations in real-world practice or differences in the degrees of patient adherence to therapy are unaccounted for in the assessment. There is no information provided on recruitment methods of sites or patients, therefore the study settings are largely unknown. There is also no information on which point in the dosing cycle (e.g., midpoint, endpoint) the serum phosphorus results measured. Since the pivotal trial demonstrated there are notable variations in the proportion of patients with serum phosphorus > LLN at the endpoint vs. the midpoint of the dosing cycle, this could greatly impact the definition of the interventions and renders inference very uncertain. The results must also be interpreted in the context of there being no harms data reported, which is an important consideration as this leaves a considerable knowledge gap in understanding the full impact of burosumab treatment. Furthermore, the patients in the burosumab cohort were comprised of both patients who had been receiving conventional therapy at baseline and those who hadn't been receiving any therapy – the magnitude of benefit due to burosumab treatment may vary within subgroups of patients based on their previous treatment patterns, which is not explored in sensitivity analyses in the cohort study. There is also no discussion of the methods used to identify the variables included in the propensity score matching. The matching itself did not achieve balance on fractures (38.0% in the burosumab cohort vs. 49.3% in the conventional therapy cohort) or the country variable, and as such any country-level differences in practice would not be controlled for in this analysis. There is also the possibility of selection bias as approximately half the patients entering the burosumab cohort had no treatment at baseline, and without treatment history it isn't known whether these patients were refractory to conventional therapy, or their disease activity levels were such that it was not needed.

There are also limitations on the generalizability of this cohort study. Less than a quarter of participants are from Canada, and therefore results may not translate directly to the characteristics of this clinical population. In addition, with an average of 245.8 days until first burosumab exposure and a mean duration between visits of 408.8 days, the burosumab cohort is treated for less time than was covered in the pivotal clinical trials and LTE extensions, limiting the applicability of these results to longer time periods. Furthermore, similar to the pivotal trial CL303, the cohort study used the same MCIDs and therefore the same limitations apply regarding the lack of an externally validated measure of clinical meaningfulness. Overall, the potential biases which may or may not be imparted by the presence of missing information greatly complicates the definition of the intervention and comparator, as well as any causal inference linking burosumab treatment to the observed results, rendering it difficult to draw conclusions regarding the relationship between burosumab treatment and patient outcomes in a real-world setting.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with XLH
Treatment	Burosumab

Component	Description
Dose regimen	For adults, the recommended dose is 1 mg/kg of body weight, rounded to the nearest 10 mg, up to a maximum dose of 90 mg, administered every four weeks.
Submitted price	Burosumab $4,514.94 per 10 mg vial $9,029.90 per 20 mg vial $13,544.84 per 30 mg vial
Submitted treatment cost	$389,427 per patient annually
Comparator	Standard of Care (SoC) comprised of: phosphate, active vitamin D (calcitriol or alfacalcidol), or no treatment
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (up to 110 years)
Key data sources	• Risk of morbidities associated with XLH for patients receiving SoC (hyperparathyroidism, parathyroidism, kidney stones, and fractures): cross-sectional study 'life-course analysis' of baseline data from Study CL303 and CL001 • Relative efficacy of burosumab versus SoC in the proportion of patients achieving serum phosphate normalization (i.e., a mean serum phosphate concentration above the lower limit of normal of 2.5 mg/dL (0.81 mmol/L)) and improvements in symptoms of pain, stiffness, and physical function (measured via WOMAC scores): Phase 3 RCT Study CL303 (burosumab versus placebo) and Phase 3b open-label extension study BUR02 (long-term follow-up of Study CL303 participants) • Relative efficacy of burosumab versus SoC in the effect of achieving serum phosphate normalization on reduction in fractures; reduction in XLH-related mortality; and reduction of SoC-related morbidities was based on assumptions from clinical experts consulted by the sponsor

Key limitations	• The comparative efficacy of burosumab versus SoC is uncertain due to an absence of head-to-head trial data versus active treatments, lack of robust long-term clinical data and assumptions used in the model are not fully supported by the clinical evidence.
	  ○ The sponsor assumed direct clinical benefits of burosumab: 100% reduction of morbidities associated with SoC active treatments and improved quality of life mapped from WOMAC scores (stiffness, pain, and fatigue) versus placebo
	  ○ The sponsor also assumed indirect benefits of burosumab: 50% reduction in mortality and reduction in the risk of fractures to the general population levels upon serum phosphate normalization
	• The model used response data (i.e. proportion of patients achieving serum phosphate normalization) after 24-weeks of treatment with burosumab (versus placebo) and did not explore waning of effectiveness despite a waning in the proportion of patients maintaining response being observed at later time points of the trial, during the open-label extensions. In the model, this results in patients accruing the same direct benefits (in quality of life and SOC-morbidities) and indirect benefits (i.e. reduction in mortality and fractures) throughout the entire time horizon, for which clinical evidence is lacking.
	• The derivation of health state utility values was associated with uncertainty due to mapping, compounded by uncertainty concerning the relative benefits of burosumab on the clinical scores used in the mapping; and it was assumed that all patients treated with burosumab would receive utility benefits regardless of treatment response. In addition, disutility due to fractures was also likely overestimated.
	• The submitted model structure was associated with methodological limitations (e.g., patients receiving SoC could not experience treatment benefit upon serum phosphate normalization) and it is uncertain whether patients on SoC would respond similarly to those trial patients who did not receive any active treatment.

Component	Description
	• Discontinuation was assumed to occur at a constant rate after the trial period and was therefore likely overestimated (and underestimating the total cost of burosumab). Burosumab is well-tolerated and clinical experts consulted by CADTH noted that the sponsor's assumption did not meet face validity and likely did not capture the proportion of patients expected to resume treatment after discontinuation in the context of chronic disease treatment (i.e. on and off treatment).
CADTH reanalysis results	• In reanalysis, CADTH assumed patients achieving response on burosumab experienced (vs. SoC): 80% reduction in incidence of fractures and 25% reduction in XLH-related mortality (aligned with clinical expert input); and a treatment waning effect of 10.2% after year 3 on treatment to reflect loss of response observed in the pivotal studies • In the CADTH base case, burosumab was more effective (incremental QALYs: 2.31) and more costly (incremental costs: $3,877,365) than SoC. This resulted in an ICER of $1,680,920 per QALY gained. • A price reduction of 98.8% would be required for burosumab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained versus SoC.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the market uptake of burosumab is likely underestimated; the drug acquisition costs of burosumab were not aligned with the submitted CUA; the derivation of the target population was uncertain; discontinuation was likely overestimated; and the sponsor's prevalence-based approach was associated with uncertainty. CADTH conducted reanalyses of the BIA by revising the market shares and adjusting the drug acquisition costs of burosumab. The CADTH reanalysis of the BIA estimated that the 3-year budget impact of reimbursing burosumab for the treatment of adult patients with XLH would be $68,007,856 in Year 1, $102,397,186 in Year 2, and $117,143,623 in Year 3, for a three-year cumulative total of $287,548,665. The drug acquisition costs of burosumab and number of eligible patients are therefore the main drivers of the difference between the 3-year drugs costs noted between the sponsor's estimates ($171,668,414) and the CADTH's base case ($288,168,029). CADTH conducted scenario analyses to address remaining uncertainty. Assuming that 68% of adult XLH patients are diagnosed and treated resulted in an increase in the estimated burosumab budget impact to $454,728,121. Assuming a lower annual discontinuation increased the budget impact to $292,616,634.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Danyaal Raza, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: May 23rd, 2024

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None