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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Burosumab (CRYSVITA)

Kyowa Kirin Limited

Indication: For the treatment of X-linked hypophosphatemia in adult and pediatric patients one year of age and older.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Table of Contents

Tables

Figures

CADTH

Abbreviations

BSC	best supportive care
EQ-5D	EuroQol 5-Dimensions
ICER	incremental cost-effectiveness ratio
NICE	National Institute for Health and Care Excellence
QALY	quality-adjusted life-year
RSS	Rickets Severity Score
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-linked hypophosphatemia

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Burosumab (Crysvita)
Study question	What is the cost-effectiveness of burosumab compared with BSC for the treatment of XLH in adults and pediatric patients (1 year of age and older) from the Canadian health care payer perspective?
Type of economic evaluation	Cost-utility analysis
Target population	Patients 1 year and older with XLH Stratified analyses by age subgroups were conducted, defined as follows: • Pediatric (age 1 year to 17 years) • Adult (age 18 years and older)
Treatment	Burosumab subcutaneous injection administered every two weeks in pediatric patients and every four weeks in adults
Outcomes	QALYs LYs
Comparators	BSC, defined based on age subgroup: • Pediatric: phosphate and vitamin D • Adult: phosphate, vitamin D, and/or calcimimetic
Perspective	Canadian public health care payer
Time horizon	Lifetime (i.e., pediatric: 99 years; adult: 60 years)
Results for base case	• The ICER of burosumab compared to BSC for the pediatric subgroup was $1,364,863 per QALY gained. • The ICER of burosumab compared to BSC for the adult subgroup was $1,119,456 per QALY gained.
Key limitations	CADTH identified the following limitations: • The comparative clinical data used to inform the model were not robust. In the pediatric model, the clinical data were based on pooling single-arm and clinical registry studies with an active-control RCT (Study 301). The BSC arm of the adult model was informed by the placebo arm of Study 303. • Long-term efficacy is uncertain. The sponsor assumed that the relative benefit of burosumab observed in short-term trials (i.e., 48 weeks to 160 weeks) could be extrapolated to a lifetime time horizon. • The direct clinical relevance of radiologically based outcome measures used in the clinical studies is unclear. It is also not clear that health states in the pediatric model, dichotomized by a total Rickets Severity Score cut-off of 1.5, accurately reflect meaningful differences in disease health states. • Implausible treatment discontinuation was assumed in the adult phase of the models. A fixed rate of discontinuation of burosumab over time was used, leading to fewer than half of patients remaining on treatment after 10 years. This is inconsistent with available evidence and clinical experts' opinions, which indicated that most patients would continue with lifelong treatment due to the chronic nature of the disorder. • Treatment-specific health-state utility values were applied in both the pediatric and adult models, with higher utility values assigned to the burosumab arm for otherwise identical health states. • An increased risk of death was assumed for patients experiencing fracture after age 50. This was based on an observational study involving a UK population. It is speculative that interventions that reduce fractures will affect mortality in this patient population.

CADTH estimate(s)	The CADTH reanalysis assumed identical utility values by health state, no discontinuation after the initial 12 months of treatment, and the use of Canadian estimates for fracture-related mortality. Based on these revisions, CADTH found that the ICER of burosumab compared to BSC for the pediatric subgroup was $2,703,146 per QALY gained, and that the ICER of burosumab compared to BSC for the adult subgroup was $3,523,922 per QALY gained. At a willingness-to-pay threshold of $50,000 per QALY, the price of burosumab would need to be reduced by 93% and 94% to be considered cost-effective in the pediatric and adult subgroups, respectively.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; RCT = randomized controlled trial; XLH = X-linked hypophosphatemia.

Drug	Burosumab (Crysvita)
Indication	Treatment of X-linked hypophosphatemia in adult and pediatric patients one year of age and older
Reimbursement request	As per indication
Dosage form(s)	10 mg/mL, 20 mg/mL, and 30 mg/mL single-use 1 mL vials
NOC date	December 5, 2018
Sponsor	Kyowa Kirin Limited

Executive Summary

Background

Burosumab (Crysvita) is a fibroblast growth factor 23 (FGF-23) blocking antibody that binds to and inhibits the biological activity of FGF-23, restores renal tubular reabsorption of phosphate, and increases serum concentration of 1,23-dihydroxyvitatmin D for patients with X-linked hypophosphatemia (XLH).[1] Burosumab is supplied in single-use vials of 10 mg/mL, 20 mg/mL, and 30 mg/mL for subcutaneous administration.[1] The recommended starting dose regimen for pediatric patients is 0.8 mg/kg of body weight rounded to the nearest 10 mg and administered every two weeks. The recommended dose regimen in adults is 1 mg/kg of body weight rounded to the nearest 10 mg and administered every four weeks. Fasting serum phosphorus should be measured every four weeks for the first three months and thereafter, as appropriate. In pediatric patients, if serum phosphorous is below the expected reference range for age, the dose may be increased stepwise in 0.4 mg/kg intervals up to a maximum of 2 mg/kg administered every two weeks. In both pediatric and adult patients, if the serum phosphorus level is above the reference range for age, the dose of burosumab should be withheld, with serum phosphorus levels reassessed four week later. Once serum phosphorus levels are below the reference range for age, burosumab may be restarted at half the dose level that was previously administered, with serum phosphorus levels reassessed every two weeks or four weeks after dose adjustment for adult and pediatric patients, respectively.[1] At the sponsor's submitted price of $4,992.29 per 10 mg/mL, and assuming the average weight reported in the respective trials,[2-4] CADTH calculated that the annual cost of treatment may range from $129,780 to $1,168,196 per pediatric patient and $454,298 to $584,098 per adult patient.

The sponsor-submitted cost-utility analyses comparing burosumab with best supportive care (BSC) in patients greater than one year of age with XLH from the perspective of the Canadian health care payer.[5] Two subgroups of interest were considered in the economic evaluation, defined by the patient's baseline age: pediatric (i.e., one year to 17 years of age) and adult (i.e., greater than or equal to 18 years of age). Note: the sponsor also submitted a subgroup analysis of patients who had a history of fracture, but the full Health Canada and reimbursement requested population shall be the focus of this review.[5] BSC was defined differently by subgroup: in the pediatric phase, BSC consisted of phosphate and vitamin D; in the adult phase, BSC consisted of phosphate, vitamin D, and/or a calcimimetic. A lifetime time horizon was used in both models, with a six-month cycle length in which future costs and benefits were discounted at a rate of 1.5%. Two Markov models were developed for the pediatric and adult phase (Figure 1).[5] The pediatric model incorporated three health states:

high Rickets Severity Score (RSS) total (≥ 1.5), low RSS total (< 1.5), and death. At the age of 18, all alive patients from the pediatric model were assumed to transition to the adult model by entering the "alive without fracture" health state. The adult model contained three health states: alive without fractures, alive with fractures, and death. Patients could transition between either alive health states or into the absorbing death state.[5] Relative treatment effects, in the form of transition probabilities, were based on the data from studies CL201, CL205, and CL301 for the pediatric model;[3,6,7] for the adult model, these were based on Study CL303.[3] Patients in the "alive with fractures" health state were assumed to have an increased mortality risk after the age of 50,[8] with Canadian general population mortality considered for all other health states.[5] Patients were assumed to receive burosumab continuously until age 18. Thereafter, a fixed proportion of patients were assumed to discontinue burosumab based on the discontinuation rate observed in Study CL303. This rate of discontinuation was applied throughout the entire lifetime of the model.[5] Utilities and costs within the same health states differed by treatment; it was assumed that patients on burosumab would incur lower costs and higher utilities for a given health state.[5] Pediatric utilities were based on expert opinion, while the utility gain for adult patients treated with burosumab was based on a conversion of the change measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale (reported in Study CL303) to EuroQol 5-Dimensions (EQ-5D) values.[3,5,9] Costs were informed by published literature and sponsor-commissioned surveys.[5]

The sponsor reported incremental cost-effectiveness ratios (ICERs) of $1,364,863 and $1,119,456 per quality-adjusted life-year (QALY) gained comparing burosumab with BSC in the pediatric and adult subgroups, respectively.[5] At a willingness-to-pay threshold of $50,000 per QALY gained, burosumab had 0% probability of being the most likely cost-effective intervention in either subgroup.[5]

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review identified several key limitations in the analysis submitted by the sponsor. First, data from several studies, including single-arm trials and a UK chart review,[5-7] were used to inform treatment probabilities in the pediatric model. In the adult model, data from Study 303 informed treatment probabilities in the economic model, in which the BSC comparator was informed by the placebo arm of that study.[5] Because patients in the placebo arm of Study 303 did not receive any active or supportive treatment, it is unclear whether this would reflect patients on BSC. There is further uncertainty in terms of the long-term clinical benefits of burosumab. As the CADTH clinical review concluded, the long-term treatment effects of burosumab are unknown. Both the pediatric and adult models assumed that the treatment effects of burosumab, based on studies lasting 48 weeks to 160 weeks, could be extrapolated to a lifetime time horizon.[5] A large magnitude of the predicted QALY gains were accrued outside of the study periods (97% for pediatric subgroup, 99% for adult subgroup). In addition, the primary end points in the pediatric clinical trials were based on radiologic outcomes with unclear correlation with patient-important outcomes. It is further unclear if the selected total RSS cut-off, used to define model health states, would accurately capture patient outcomes and all meaningful health states. Similarly, the clinical significance of fracture[5] are unclear, given that they do not correlate with outcomes that are important to patients, such as pain (see clinical report) and are exploratory outcomes in Study CL303.

A proportion of patients discontinued burosumab in Study CL303, which was 48 weeks in duration.[3] However, it is unlikely that the study's reported rate of discontinuation (4.05%

every six months) would continue to apply over a lifetime in adults treated with burosumab. The clinical experts consulted by CADTH confirmed that XLH is a chronic disease, and patients are likely to continue use of burosumab over their lifetime, given its favourable adverse event profile and the limited treatment alternatives available. Applying a fixed discontinuation rate over a lifetime would underestimate the drug costs for burosumab.

The health-state utility values in both the pediatric and adult models were treatment-specific. This is contradictory to the CADTH Guidelines for the Economic Evaluation of Health Technologies, which recommend utilities be associated with health states to increase transparency.[10] In all instances, higher utility values were assigned to the burosumab arm rather than the BSC arm for the same health state, favouring burosumab.

A mortality benefit was assumed for patients treated with burosumab through a reduced fracture-related mortality risk after the age of 50 years, using data from an observational study of the general UK population.[8] It is unknown if treatment to reduce fractures in this patient population would affect mortality.

CADTH attempted to address some of these issues by assuming the same utility values in each health state regardless of treatment strategy, applying a discontinuation rate only in the first 12 months in the adult phase of the models, and using fracture-related mortality rates based on Canadian data.[11] Significant uncertainty remains in the reanalyses, given that both the short- and long-term comparative effectiveness of burosumab compared with BSC is uncertain.

Conclusions

CADTH's findings were aligned with the sponsor's: burosumab was found not to be a cost-effective option at conventionally accepted willingness-to-pay thresholds (e.g., $50,000 per QALY). In the CADTH reanalyses, compared with BSC, the ICERs for burosumab were more than $2.7 million per QALY in pediatric populations and more than $3.7 million per QALY in adult populations. Price reductions of 93% and 94%, respectively, would be required for the ICER of burosumab to fall below $50,000 per QALY when compared with BSC.

The ICER was highly sensitive to the assumptions regarding discontinuation rate because of the high cost of burosumab. CADTH was unable to address the uncertainty in the clinical data because of the paucity of literature establishing differences in clinically important outcomes and the lack of long-term data. Sensitivity and scenario analyses addressing some of these uncertainties resulted in a larger ICER (e.g., when no difference in fracture risk was assumed, the ICER increased to more than $4.0 million per QALY in the adult subgroup). As such, the ICER is highly uncertain; if modelled effectiveness is overestimated, the ICER of burosumab may be larger.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted two separate cost-utility analyses comparing burosumab with BSC for the treatment of XLH in pediatric and adult patients.[5] BSC was defined differently by age; in the pediatric phase of the model, BSC consisted of treatment of all patients with phosphate and vitamin D; in the adult phase, only a proportion of patients were treated with phosphate, vitamin D, and/or calcimimetic, based on utilization reported in the sponsor's commissioned surveys.[5] The analyses were conducted from the Canadian public payer perspective with a lifetime time horizon, with cycles defined as every six months. Costs and clinical outcomes (QALYs and life-years) were discounted at 1.5% per annum.[5]

The model structure differed by the patients' ages. The pediatric phase of the model had the following health states: high RSS total (≥ 1.5), low RSS total (< 1.5), and death. At the age of 18, all patients who remained alive entered the adult phase of the model and were assumed to transition to the "alive without fracture" health state. Health states in the adult model included alive without fractures, alive with fractures, and death.[5] For the pediatric model, the transition probability inputs for the burosumab arm were based on the pediatric studies (Study CL201, Study CL205, and Study CL301);[3,6,7] the former two were single-arm studies. Transition probabilities for the BSC arm of the pediatric model were based on combined data from a UK chart review and Study CL301.[4,5] At age 18 (in both pediatric and adult subgroups), transition probabilities (e.g., probabilities of developing new fractures and probabilities of healed fractures) for both burosumab and BSC were based on Study CL303.[3] Adult patients could incur one or more fracture event over time, based on the probability of developing a fracture; at which point, they entered the alive with fracture health state. These patients would transition back to alive without fracture based on the probability of healed fracture.[5] Patients in the alive with fractures state were assumed to have an increased mortality risk after the age of 50,[8] with Canadian general population mortality considered for all other health states.[5] Adverse events were not considered in the economic model.[5] Patients were assumed to receive burosumab continuously until age 18 (i.e., no pediatric patients discontinued from treatment). From the age of 18 onwards, a proportion of patients (4.05% every six months) discontinued burosumab, based on the discontinuation rate reported in Study CL303 and applied in perpetuity.[3] Patients who discontinued were assumed to be managed with BSC.[5]

Health-state utilities were assigned to current health states (i.e., RSS or fracture health states) that differed by age. Utilities for pediatric health states were based on the values reported in the National Institute for Health Care and Excellence (NICE) evaluation report on burosumab.[12] The utility values for pediatrics came from a sponsor-conducted utility study in which, using the EuroQol 5-Dimensions 5-Levels, six UK clinicians with experience treating XLH valued the quality of life of patients with XLH at the ages of 18 years, 40 years, and 60 years, based on health-state vignettes.[5] After the age of 18 years, a baseline XLH utility of 0.648 was applied for all patients, based on literature.[13] An additional disutility of –0.108 was applied for the incident year of each fracture event.[14] The model also assumed that adult patients treated with burosumab would incur an additional utility benefit of 0.044 at each cycle. This value was determined by mapping the change in WOMAC scores in Study CL303 to EQ-5D values.[3,5,9]

The average dose of burosumab was dependent on patient weight and was assumed to increase with age based on Canadian normal population weights from Centers for Disease Control and Prevention reference data. In the pediatric model, the average dose was assumed to be 0.82 mg/kg in the first cycle and 0.86 mg/kg thereafter, based on the dose observed in Study CL301.[4] For adults, the average doses were assumed to be 0.96 mg/kg, 0.94 mg/kg, and 0.90 mg/kg for the first, second, and subsequent doses, as observed in Study CL303.[3] An additional subcutaneous administration cost of $4.01 (derived from the Ontario Schedule of Benefits) was also considered for burosumab.[15] Before age 18, the dose and frequency of BSC treatment (oral phosphate and vitamin D) was derived from a treatment guideline for patients with XLH.[16] The dose for BSC was similarly dependent on patient weight, which was assumed to increase with age. Other costs, such as those associated with surveillance; pain and mobility (walking devices and physical therapy); surgery; fractures; and terminal care were also included in the model, and varied by RSS health state and by treatment (burosumab versus BSC).[5] For the first three months, more frequent surveillance and monitoring were assumed for burosumab, based on the monitoring recommendation in its Health Canada indication;[1] thereafter, it was assumed that the surveillance and monitoring schedule would be identical to the monitoring schedule for BSC (except with regard to serum and urinary lab measures, renal ultrasound, and radiography). For BSC, the monitoring frequencies were obtained from treatment guidelines and a NICE evaluation report.[12,17] In adults, burosumab was associated with a 50% offset in mobility and surgical costs, based on the sponsor's assumptions, and a 72% offset in pain medication costs, based on Study CL303.[3,5]

Sponsor's Base Case

In the sponsor's base-case analysis for a pediatric population, burosumab was associated with an additional 5.78 QALYs and $7,893,946 compared to BSC (disaggregated cost results are presented in Table 13).[5] The ICER for burosumab versus BSC was $1,364,863 per QALY gained (Table 2).[5]

For the pediatric subgroup, the cost-effectiveness acceptability curves based on 1,000 iterations found that 9% of the results fell below $1,000,000 per QALY gained. None of the iterations fell below a $250,000 per QALY threshold (Figure 2).[5]

Table 2: Summary of Results of the Sponsor's Base Case (Pediatric Subgroup)

	Drug and administration cost ($)	Other costs ($)[a]	Total costs ($)	Incremental cost of burosumab ($)	Total QALYs	Incremental QALYs of burosumab	Incremental cost per QALY
Burosumab	8,276,035	755,084	9,031,119		32.07		
BSC	29,944	1,107,229	1,137,173	7,893,946	26.29	5.78	1,364,863

BSC = best supportive care; QALY = quality-adjusted life-year.

[a] Other costs include those related to surveillance, fracture, pain and mobility, surgery and terminal care. A detailed cost breakdown can be found in Appendix 4.

Source: Sponsor's pharmacoeconomic submission.[5]

In the sponsor's base-case analysis for an adult population, burosumab was similarly more effective (3.19 additional QALYs) and more costly ($3,574,790) (disaggregated cost results are presented in Table 14). The ICER for burosumab compared with BSC was $1,119,456 per QALY gained (Table 3).[5]

For the adult subgroup, cost-effectiveness acceptability curves of 1,000 iterations reported that 17% of the results fell below $1,000,000 per QALY gained. Similarly, no results fell below the $250,000 per QALY threshold (Figure 3).[5] The acceptability curves for both models can be found in Appendix 4.

Table 3: Summary of Results of the Sponsor's Base Case (Adult Subgroup)

	Drug and administration cost ($)	Other costs ($)[a]	Total costs ($)	Incremental cost of burosumab ($)	Total QALYs	Incremental QALYs of burosumab	Incremental cost per QALY
Burosumab	3,932,740	695,346	4,628,086		19.68		
BSC	12,220	1,041,077	1,053,297	3,574,790	16.49	3.19	1,119,456

BSC = best supportive care; QALY = quality-adjusted life-year.

[a] Other costs include those related to surveillance, fracture, pain and mobility, surgery and terminal care. A detailed cost breakdown can be found in Appendix 4.

Source: Sponsor's pharmacoeconomic submission.[5]

Summary of Sponsor's Sensitivity Analyses

No additional sensitivity analyses were reported by the sponsor.

A subgroup analysis was performed, limited to adult patients who had a history of fracture prior to starting treatment with burosumab, according to a post hoc subgroup analysis of Study CL303. Burosumab was associated with an additional 5.65 QALYs and $3,971,352 compared to BSC. The ICER for burosumab was reduced to $702,672 per QALY gained compared to BSC (Table 15).[5]

Limitations of Sponsor's Submission

- **Comparative effectiveness estimates are uncertain.** There is substantial uncertainty regarding the comparative effectiveness estimates of burosumab compared with BSC that were used to inform the pediatric model. The clinical effects of burosumab were based on two single-arm studies (CL201 and CL205)[6,7] that were pooled together with the open-label Study CL301,[4] while the transition probabilities for BSC were based on combined data from a UK chart review and Study CL301.[4,5] The use of chart review data and the pooling of methodologically different clinical trials is inappropriate. For instance, Study CL201 was based on a dose of burosumab not approved by Health Canada. CADTH was unable to address this limitation. Although Study CL301 was the only study that compared burosumab against BSC, it enrolled only patients with a high total RSS at baseline.[18] There was no comparative clinical evidence to inform the transition probabilities for patients in the low RSS state.

  Data from Study CL303 informed the comparative effectiveness estimates of burosumab compared with BSC in the adult model.[5] Specifically, the transition probabilities for BSC were informed directly by the results of the placebo arm of that trial. As patients in the placebo arm of Study CL303 did not receive any active treatment, it remains unclear whether patients on BSC would, in fact, respond similarly to those in the placebo arm of that trial.
- **Uncertainty in long-term efficacy.** The models assumed that the benefits of burosumab in short-term trials (48 weeks to 160 weeks in duration) could be extrapolated to a lifetime time horizon (i.e., 99 years for the pediatric subgroup; 60 years for the adult subgroup).

Only 0.09 QALYs in the pediatric subgroup and 0.07 QALYs in the adult subgroup were gained in the first year, with the majority of the QALYs gained from burosumab accrued outside the trial period (approximately 3.10 QALYs in pediatrics and 5.58 QALYs in adults). This finding is concerning because, as per the CADTH clinical review, the long-term efficacy and safety of burosumab has not been established.[3] Significant uncertainty exists in the true long-term effectiveness of burosumab, which further contributes to uncertainty in the cost-effectiveness estimates. If efficacy attenuates over time, the ICER may be underestimated. CADTH was unable to address this limitation of the submitted model.

- **Conceptualization of the economic model:** The RSS total is a radiographically assessed end point used in the pediatric studies to assess the severity of rickets and bowing (0 = no evidence of rickets and 10 = most severe).[19] It is also used as a health state in the pediatric model. However, the RSS total is not used in clinical practice, according to the clinical experts consulted for this review, and does not have a defined minimal clinically important difference. The model dichotomized the RSS total into above and below 1.5,[5] but it is not clear that this accurately represents all meaningful disease states; the clinical experts consulted by CADTH indicated that a score of 1.5 is relatively mild. The CADTH clinical report noted that, while the RSS total demonstrated statistically significant improvements with burosumab, it is uncertain how these translated into patient-important outcomes.

  There were no clinical data on patients aged 13 years to 18 years. Although this adds further uncertainty to the potential efficacy of the drug, the clinical experts consulted by CADTH suggested that slower growth for girls is expected at this age, and would be associated with less healing of rickets, whereas slower growth for boys is expected at a slightly older age. Once growth is stabilized, patients would be expected to respond more similarly to adults. This brings forth questions concerning whether this age group is most accurately modelled in the pediatric model, which is based on RSS-defined health states.

  In the adult phase of both subgroups, Study CL303 was used to inform the proportion of patients developing new fractures and the probability of healed fractures.[5] The clinical relevance of healing fractures is not known, and does not appear to be related to pain scores (see clinical review). Finally, while data pertaining to effectiveness were obtained from Study CL303, these were not primary outcomes (exploratory outcomes examined post hoc).[5] Within the study, new fractures were reported in one patient treated with burosumab and in two patients on placebo by week 24 (see clinical report).

  CADTH was unable to address this limitation of the submitted model.

- **Assumption of discontinuation in the adult model.** A small proportion of patients (i.e., 1.5% at 24 weeks) discontinued treatment in Study CL303 for reasons that were not reported, but not due to adverse events.[3] While initial treatment discontinuation is reasonable to assume within the economic model, it is not established that discontinuation would occur at the same rate over a lifetime. By applying a constant rate of discontinuation (assumed to be 4.05% every six months), the model predicted that fewer than half of patients (45%) would still be on burosumab after 10 years. The CADTH clinical experts confirmed that XLH is a chronic disease, and patients are likely to continue treatment, given that limited treatment alternatives exist. Furthermore, as the clinical report noted, burosumab is well tolerated (notably, adverse events for burosumab-treated patients were not included in the model, an approach that was deemed appropriate by the clinical experts consulted by CADTH, given the low rate and severity of adverse events observed in the trials). By assuming a fixed discontinuation rate over a lifetime, drug costs for burosumab are underestimated.

- **Application of treatment-specific utility values.** Several methodological issues were noted with the derivation of utilities. As a result, the utilities used in the sponsor's base case are associated with substantial uncertainty. Health-state utility values in the sponsor's submitted pediatric model were based on opinions from six experts rather than the trial data.[5] The accuracy of the health-state descriptions within the health vignettes is uncertain. Utility values were elicited for patients at 18 years, 40 years, and 60 years of age, with utility values then extrapolated to a pediatric population.[5] Further, the utility values were treatment-specific, meaning that for an identical health state, a different utility value would be associated, depending on treatment (i.e., burosumab and BSC). The use of treatment-specific utility values is not transparent, because it is unclear where the added clinical benefit is coming from, given that patients are otherwise in an identical health state.[10]

  In the adult model, an additional utility benefit from treatment with burosumab was incorporated based on the changes in WOMAC scores reported in Study CL303 between baseline values and week 48 values.[5] Specifically, the WOMAC scores were converted to EQ-5D values using a conversion algorithm from literature.[9] This algorithm is unvalidated, which adds uncertainty given that its predictive value is unclear. An additional utility gain of 0.044 was assigned to the burosumab arm per cycle in the sponsor's model for patients in the adult phase. Although Study CL303 reported a favourable improvement in WOMAC scores in the placebo arm (mean changes at 24 weeks were –0.77 for the stiffness score and –0.97 for the physical function score),[3] this was not considered in the sponsor's model. This inconsistent application of treatment-specific utilities would favour burosumab, as it would produce higher expected utilities. As noted previously, the use of treatment-specific utility values is contradictory to CADTH guidelines that recommend utilities be associated with health states.[10]
- **Assumption of reduction in mortality by reducing risk of fractures.** The post hoc analysis of Study CL303 suggested an improvement in healed fractures (although no statistical analysis testing was performed). The submitted economic model assumed that there would be an increased mortality risk for patients experiencing a fracture after the age of 50.[5] This risk was informed by data from a UK population-based observational study.[8] Using observational data to estimate fracture-associated mortality does not account for potential confounders (for example, frailty that may be causal to both fractures and mortality). Randomized controlled trials of osteoporosis treatments have suggested there may be a reduction in mortality with treatment, but this effect is small (relative risk = 0.89), and is most prominent in study populations with higher mortality rates.[20] It is uncertain that interventions that reduce fractures in this specific patient population will have an impact on mortality; and if mortality benefits do occur, they are likely to be of lower magnitude than used in the sponsor's model.
- **Assumption of treatment-specific costs.** Mobility and surgical costs were assumed to be 50% less for burosumab-treated adults without supporting evidence.[5] Although a potential argument can be made that costs are reduced given patients with fractures healed faster with burosumab compared to placebo in Study CL303, the clinical impact of this observation and its effect on health care utilization is unknown. Similarly, pain medication was offset by 72% for patients on burosumab in the sponsor's model. Although the sponsor claims that this percentage was informed by Study CL303,[3] the use of pain medication was reported in 69.1% and 66.2% of patients on burosumab at baseline and week 24, respectively, whereas for patients on placebo, its use was reported in 66.7% and 60.6% of patients at baseline and week 24, respectively. The sponsor's claims do not appear to be supported by the available study evidence. These

assumptions together would favour burosumab; however, as these costs were relatively small compared to the drug costs of burosumab, they are unlikely to have an impact on the model. CADTH conducted scenario analyses in which treatment-specific costs for which no trial data were available to support the sponsor's assumptions (i.e., mobility and surgical costs in adults) were removed.

- **Use of an arbitrary coefficient of variation.** For the majority of model parameters within the sponsor's submitted model, standard errors that defined the probability distribution were set arbitrarily rather than reflecting the underlying data sources. The standard error for a majority of the utility estimates and the transition probabilities in the adult model were fixed at 10% of the mean estimates, whereas the standard error for cost estimates in both models was mostly fixed at 25% of the mean estimates. Therefore, the uncertainty observed in the probabilistic results may not fully reflect the true uncertainty expected around model parameters. The arbitrary assumption in defining probability distributions is inappropriate, as parameters with low sensitivity but higher uncertainty should affect the model's output more than more sensitive parameters that are estimated more precisely.[10]

CADTH Reanalyses

CADTH conducted the following reanalyses to address some of the key limitations described above. The analyses were conducted probabilistically based on 5,000 iterations.

- For both the pediatric and adult models, treatment-specific utilities were removed.
- In the adult phases of both pediatric and adult subgroups, fracture-related mortality was changed to reflect Canadian estimates. The selected study was a large, prospective cohort study that reported the added risk of non-hip, non-vertebral fractures on mortality.[11] This may still overestimate the true benefit, as it cannot account for confounders, and reflects a different patient population. A sensitivity analysis of no difference in mortality (relative risk = 1) is also presented in Appendix 4.
- In the adult phase of both pediatric and adult subgroups, discontinuation was only allowed for the first two cycles (i.e., no treatment discontinuation after 12 months) as per discontinuation rates reported in the double-blind, open-label extension of Study CL303.[3]

In the CADTH base-case reanalysis, the ICER for burosumab was $2,703,146 per QALY gained in the pediatric subgroup, and $3,523,922 per QALY gained in the adult subgroup when compared to BSC (Table 4). The most significant change in the ICER was noted when discontinuation was capped at the first year, as it led the ICER to increase by more than $2 million per QALY gained. Other changes led to smaller increases in the ICER. At a willingness-to-pay threshold of $50,000 per QALY gained, burosumab had 0% probability of being the most likely cost-effective intervention in either subgroup.

It should be noted that due to inherent limitations with the clinical data, these reanalyses do not account for the significant uncertainty in the true comparative clinical benefit of burosumab. Further uncertainty exists due to how data were incorporated into the model, the overall conceptualization of the model, and assumptions that affect costs and effects over both short- and long-term time horizons. Many of the assumptions may be favourable to burosumab; it is plausible that the CADTH reanalysis may underestimate the true ICER.

Table 4: CADTH Reanalysis of Limitations

	Description	Sponsor's base-case value	CADTH value	Burosumab vs. BSC		
				Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
Pediatric subgroup						
	Sponsor's base case	Reference		7,893,946	5.78	1,364,863
1	Utility values	Treatment-specific utilities applied	No treatment-specific utilities	7,985,769	4.94	1,617,872
2	Fracture-related mortality	SMRs: 4.32 (males) and 2.73 (females)	SMRs: 1.22 (males) and 1.27 (females)	7,975,510	5.82	1,370,171
3	Discontinuation	Constant rate of discontinuation of 4.05%	Rate of discontinuation only applied during the first year Cycle 1: 1.5% Cycle 2: 5.9%	16,234,816	7.99	2,031,500
	CADTH base case (1 + 2 + 3)			**16,238,620**	**6.01**	**2,703,146**
Adult subgroup						
	Sponsor's base case	Reference		3,574,790	3.19	1,119,456
1	No utility difference by treatment strategy	Treatment-specific utilities applied	No treatment-specific utilities	3,702,447	2.76	1,339,194
2	Use of Canadian fracture-related mortality	SMRs: 4.32 (males) and 2.73 (females)	SMRs: 1.22 (males) and 1.27 (females)	3,660,347	3.14	1,166,424
3	No discontinuation after trial period	Constant rate of discontinuation of 4.05%	Rate of discontinuation only applied during the first year of adult model Age 18 years: 1.5% Age 18.5 years: 5.2%	11,466,437	4.82	2,381,377
4	**CADTH base case (1 + 2 + 3)**			**11,465,179**	**3.25**	**3,523,922**

BSC = best support care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SMR = standardized mortality ratio; vs. = versus.

CADTH undertook the following additional scenario analyses of the CADTH base case:

- Assumption that all pediatric patients enter the model in the high RSS state. CADTH clinical experts stated that burosumab is likely to be initiated in pediatric patients with more severe rickets (i.e., RSS total > 2).
- Prior history of fracture (conducted on the adult subgroup only). The sponsor performed a subgroup analysis on adult patients with a prior history of fracture. Although this subgroup was identified post hoc in Study 303 and consists of a small sample size (n = 29 per study arm), the model was rerun based on the CADTH's base-case changes (i.e., no utility difference by strategy, use of Canadian fracture-related mortality, and no discontinuation after trial period).
- Removal of dental and assistive devices costs in both the adult and pediatric models. Some jurisdictions do not cover these.

To address structural and parameter uncertainties with the submitted model, CADTH further conducted the following scenario analysis:

- assumption of no difference in the probability of developing new fracture, as the clinical report suggested that it is unknown whether burosumab treatment would prevent fractures (in Study CL303, new fractures were reported in one patient treated with burosumab and in two patients on placebo by week 24; a scenario analysis was performed assuming identical probability of developing new fracture between treatments)
- assumption of no fracture-related mortality in adults experiencing a fracture at age greater than 50 (standardized mortality ratio = 1)
- same mobility and surgical costs (i.e., no reduction in mobility and surgical costs for burosumab compared to BSC)
- same surveillance cost, as clinical experts consulted by CADTH indicated similar monitoring procedures would be performed
- assumption of no treatment discontinuation
- replacing the treatment costs for BSC with no treatment in the adult phase of the model, aligning fully to the comparator that was studied in Study CL303.

Full results of the CADTH scenario analyses are presented in Table 17 in Appendix 4. Most results were robust and similar to the CADTH base case, except when the same probability of developing new fracture was used, which increased the ICER in the adult subgroup to greater than $4.0 million per QALY gained. In the scenario that used the assumption that treatment initiation for pediatric patients was at a high RSS state lowered the ICER to $2.6 million per QALY gained.

For the CADTH base case, price reduction analyses were undertaken by subgroup (Table 5). The results show that a price reduction of 93% and 94% would be required to bring the ICER under $50,000 per QALY for the pediatric and adult subgroups, respectively.

Table 5: CADTH Reanalysis Price Reduction Scenarios

ICERs of burosumab versus BSC ($ per QALY)		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
Pediatric subgroup		
Submitted	1,364,863	2,703,146
25% reduction	1,012,082	1,991,773
50% reduction	653,368	1,280,400
60% reduction	509,882	995,851
70% reduction	366,397	711,302
80% reduction	220,037	426,753
90% reduction	79,426	124,204
91% reduction	65,077	113,749
92% reduction	50,728	85,294
93% reduction	36,380	56,839
94% reduction	22,031	28,384
Adult subgroup		
Submitted	1,119,456	3,523,922

ICERs of burosumab versus BSC ($ per QALY)		
25% reduction	840,057	2,580,732
50% reduction	523,534	1,637,542
60% reduction	396,925	1,260,265
70% reduction	270,317	882,989
80% reduction	141,172	505,713
90% reduction	17,099	128,437
91% reduction	4,438	90,709
92% reduction	Burosumab dominates	52,982
93% reduction	Burosumab dominates	15,254
94% reduction	Burosumab dominates	Burosumab dominates

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Issues for Consideration

According to the clinical experts consulted, the convenience of less frequent administration of burosumab may improve adherence compared with oral BSC. However, it is uncertain how patient preference for mode of administration (i.e., oral versus subcutaneous injections) may affect compliance. The submitted economic model assumed full compliance in both treatment arms.[5]

Patient Input

Patient input was received from the Canadian Organization for Rare Disorders, with support from the XLH Network. Many patients and caregivers were concerned about the frequency of administration with current treatments. Since burosumab is expected to be a less frequent injection, this was a potential advantage that has not been incorporated in the model.

Respondents who had experience with burosumab were overwhelmingly positive about its impact on pain, fractures, dental problems, and mobility. The cost impact of burosumab on these aspects has been considered in the sponsor's submitted economic evaluation despite limited evidence from the available clinical trial evidence to support the sponsor's claims regarding resource use.

Most respondents also expected that burosumab would stop disease progression because it addresses the underlying cause of the disease. This was partly addressed in the model by the lower probabilities associated with entering the high RSS and alive with fractures states for burosumab. In addition, the probability of healed fracture was 10 times higher for burosumab in the model (45.8% for burosumab versus 4.8% for BSC).

Conclusions

CADTH's findings were aligned with the sponsor's: burosumab was found not to be a cost-effective option at conventionally accepted willingness-to-pay thresholds (e.g., $50,000 per QALY). In the CADTH reanalyses, compared with BSC, the ICERs for burosumab were more than $2.7 million per QALY in pediatric populations and more than $3.7 million per QALY in adult populations. Price reductions of 93% and 94%, respectively, would be required for the ICER of burosumab to fall below $50,000 per QALY when compared with BSC.

The ICER was highly sensitive to the assumptions regarding discontinuation rate because of the high cost of burosumab. CADTH was unable to address the uncertainty in the clinical data because of the paucity of literature establishing differences in clinically important outcomes and the lack of long-term data. Sensitivity and scenario analyses addressing some of these uncertainties resulted in a larger ICER (e.g., when no difference in fracture risk was assumed, the ICER increased to more than $4.0 million per QALY in the adult subgroup). As such, the ICER is highly uncertain; if modelled effectiveness is overestimated, the ICER of burosumab may be larger.

Appendix 1: Cost Comparison

The comparators presented in Table 6 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are sponsor list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 6: CADTH Cost Comparison Table for X-Linked Hypophosphatemia

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Average drug cost per administration ($)	Average annual drug cost ($)
Burosumab (Crysvita)	10 mg/mL 20 mg/mL 30 mg/mL	Single-use vial	4,992.2900[a] 9,984.5800 14,976.8700	**Pediatric:** 0.8 mg/kg SC[b] every 2 weeks.[c] The minimum starting dose is 10 mg up to a maximum dose of 90 mg. **Adult:** 1 mg/kg SC[b] every four weeks[d] up to a maximum dose of 90 mg	**Pediatric:** 4,992.29 to 44,930.61 **Adult:** 34,946.03 to 44,930.61[e]	**Pediatric:** 129,780 to 1,168,196[f] **Adult:** 454,298 to 584,098[g]

SC = subcutaneous.

[a] Sponsor-submitted price.

[b] Rounded to the nearest 10 mg.

[c] After initiation of treatment, fasting serum phosphorus should be measured every 4 weeks for the first 3 months of treatment and as appropriate thereafter. If serum phosphorus is below the reference range for age, dose may be increased. The dose should be increased stepwise in 0.4 mg/kg intervals up to a maximum of 2 mg/kg, every 2 weeks. If serum phosphorous is above the reference range for age, withhold the next dose, and reassess serum phosphorous levels in 4 weeks; once serum phosphorus is below the reference range for age, restart treatment at half the previous dose level. Reassess serum phosphorus level 4 weeks after dose adjustment. If level is below reference range for age, dose may be increased as described above.

[d] After initiation of treatment, fasting serum phosphorus should be measured monthly for the first three months of treatment and as appropriate thereafter. If serum phosphorous is above the normal range, withhold the next dose, and reassess serum phosphorous levels in 4 weeks. Once serum phosphorus is below the normal range, restart treatment at half the previous dose level, up to a maximum of 40 mg. Reassess serum phosphorus level 2 weeks after dose adjustment.

[e] Based on an average patient weight of 70.7 kg, as reported in Study CL303.[3]

[f] Based on patients receiving 26 administrations per year. Assumes no doses are held due to serum phosphorous being above the normal range.

[g] Based on patients receiving 13 administrations per year. Assumes no doses are held due to serum phosphorous being above the normal range.

Table 7: CADTH Cost Comparison Table for X-Linked Hypophosphatemia Treatments Not Currently Indicated

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average drug cost per administration ($)	Average annual drug cost ($)
Phosphates						
Sodium phosphates (Phoslax)	125 mg/mL[a]	Oral solution	0.1018 per gram[b]	**Pediatric:** elemental phosphate 20 mg/kg/day to 40 mg/kg/day (divided into 5 doses)[c] **Adult:** 500 mg elemental phosphate twice or three times daily[c]	**Pediatric:** 0.04 to 0.08[d] **Adult:** 0.10 to 0.15	**Pediatric:** 15 to 31 **Adult:** 37 to 56
Sodium Phosphate (Jamp-Sodium Phosphate)	500 mg	Oral efferves-cent tablet	1.4010[e]	**Pediatric:** elemental phosphate 20 mg/kg/day to 40 mg/kg/day (divided into 5 doses)[c] **Adult:** 500 mg elemental phosphate twice or three times daily[c]	**Pediatric:** 1.40 to 2.80[d] **Adult:** 2.80 to 4.20	**Pediatric:** 511 to 1,023 **Adult:** 1,023 to 1,534
Vitamin D						
Vitamin D alfacalcidol (One-Alpha)	0.25 mcg 1 mcg	Capsule	0.5211 1.5600	Starting dose is 1 mcg daily up to maximum dose of 3 mcg daily[g]	1.56 to 4.68	569 to 1,708
	2 mcg/mL	Oral drops	5.8710 per 10 mL vial[f]		0.29 to 0.88	107 to 321
	2 mcg/mL	Injectable solution	10.0350 per 0.5 mL ampoule[f] 20.0680 per 1 mL ampoule[f]	6 mcg to 12 mcg weekly[g]	8.60 to 17.20	3,131 to 6,261
Calcitriol (Calcitriol-Odan)	0.25 mcg 0.50 mcg	Capsule	0.4682 0.7446	**Pediatric:** 20 nanograms/kg/day to 30 nanograms/kg/day	**Pediatric:** 0.74 to 1.49[d] **Adult:** 0.47 to 1.49	**Pediatric:** 271 to 544 **Adult:** 171 to 544

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Average drug cost per administration ($)	Average annual drug cost ($)
				(divided in two doses per day)[c] **Adult:** 0.25 mcg to 0.5 mcg once or twice per day[c]		
Calcimimetic						
Cinacalcet hydrochloride (Sensipar)	30 mg 60 mg 90 mg	Tablet	10.1947 18.5900 27.0517	15 mg to 60 mg daily[g,h]	5.10 to 18.59	1,860 to 6,785

Note: All prices are from the Ontario Drug Benefit Formulary (accessed September 2019)[21] unless otherwise indicated and do not include dispensing fees.

[a] Source of Phoslax strength: BC Children's Hospital.[22]

[b] Source: BC Pharmacare Formulary (accessed September 2019).[23]

[c] Source: Clinical experts consulted by CADTH for this review.

[d] Based on an average patient weight of 20.6 kg, as reported in Study CL301.[4]

[e] Alberta Interactive Drug Benefit List (accessed October 2019).[24]

[f] Source: IQVIA database (accessed September 2019).[25]

[g] Source: Canadian Public Health Association Therapeutic Choices: Vitamin D product monograph.[26]

[h] Dose is based on parathyroid hormone levels. Not indicated in pediatric patients.

Appendix 2: Additional Information

Table 8: Submission Quality

	Yes/good	Somewhat/ average	No/poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”	An additional request was made to the sponsor for outstanding references to the report.		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 9: Authors’ Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

☒ Adaptation of global model/Canadian model done by the sponsor

☐ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

Burosumab injection has been reviewed by the UK's NICE for the pediatric indication.[12,27] It was determined by Germany's Institute for Quality and Efficiency in Health Care to be an orphan drug and approved for the treatment of hypophosphatemia. The financial impact of the drug is currently under review.

Table 10: Other Health Technology Assessment Findings

	NICE (2018)
Treatment	Burosumab injection, 0.8 mg/kg administered subcutaneously every 2 weeks[27]
Price	• 10 mg vial £2,992 (CDN$5,187)[a12] • 20 mg vial £5,984 (CDN$10,373)[a12] • 30 mg vial £8,976 (CDN$15,560)[a12]
Similarities with CADTH submission	• Discount rate of 1.5%[27] • Data from studies CL205, CL201, and CL301 and a UK chart review used to inform transition probabilities[27] • AE costs not included[27] • Standard of care costs included vitamin D and oral phosphate[12]
Differences with CADTH submission	• Target population was children and young people only[27] • Different model structure: Markov model structure with four health states defined by RSS (healed, mild, moderate, severe); no adult health states[27] • One-year cycle length • Treatment assumed to stop at age 16 years for girls and age 17 years for boys[12] • Upon stopping treatment, patients remain in their current health state for the rest of the model time horizon[27] • Utilities values from NICE report were used to inform the CADTH report, but because different health states were used, these were converted to fit with the CADTH model structure[5] • Caregiver disutility incorporated into model[27]
Sponsor's results	Treatment with burosumab yielded 10.304 more QALYs compared with standard of care (total costs and ICER redacted).[12]
Issues noted by the review group	• Use of 1.5% discount rate inappropriate. Discount rate of 3.5% should have be used.[27] • No cost to AEs. A cost of £5 should have been added for injection-site reaction. • Burosumab transition probabilities did not account for competing risk between modelled health states. • Uncertainty in pooling of trials due to different study populations.[27] • No clinical evidence for people aged 13 years to 17 years adds uncertainty to clinical efficacy.[27] • Uncertainty in long-term efficacy.[27] Assumption of lifetime disease stabilization is unrealistic.[27] Treatment stopping age should be 15 years for girls and17 years for boys.[27] • Utilities do not match those reported in published vignette study. • Lack of convergence between probabilistic and deterministic results.[12]
Results of reanalyses by the review group (if any)	• ICER of £149,565 (CDN$259,271)[a] per QALY gained for burosumab compared with standard of care, using conservative stopping ages (16 years in girls and 17 years in boys) and no caregiver disutility[27] • ICER of £112,517 (CDN$195,048)[a] per QALY gained for burosumab compared with standard of care, using optimistic treatment stopping ages (14 years in girls and 16 years in boys) and including caregiver disutility[27]
Recommendation	Burosumab is recommended, within its marketing arrangement, for treating X-linked hypophosphatemia in children aged 1 year and over, and in young people with growing bones, with radiographic evidence of bone disease.[27]

AE = adverse event; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year; RSS = Rickets Severity Score.

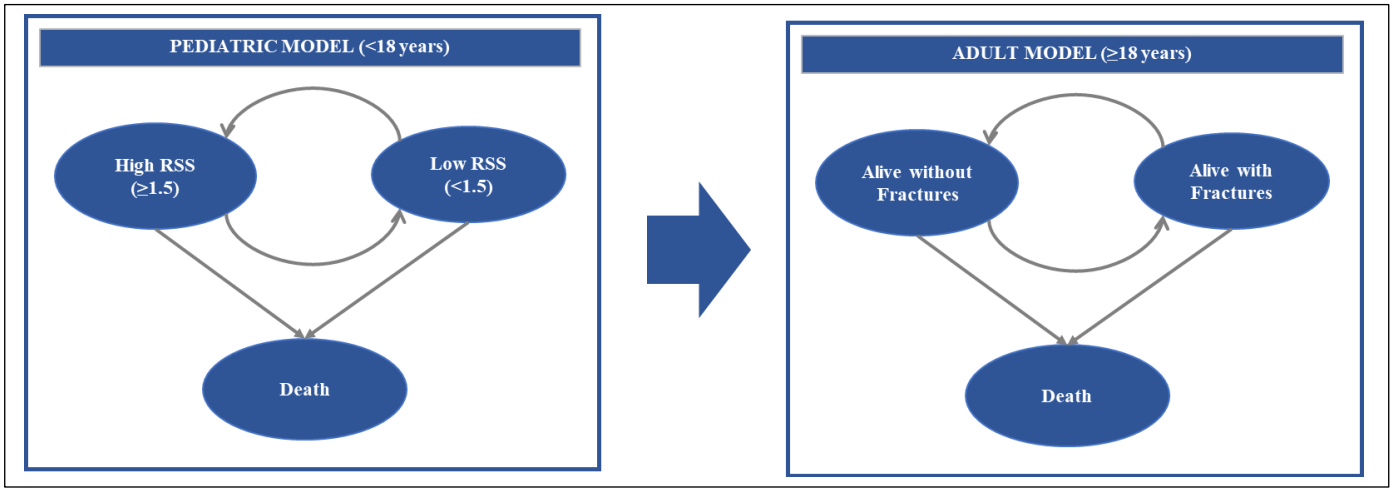
[a] Rate: £1 = CDN$1.7335, based on Bank of Canada historical exchange rate for May 2018.[28]

Appendix 4: Reviewer Worksheets

Sponsor's Model Structure

Two Markov models (pediatric and adult) with six-month cycles were developed.[5] Details of the Markov structure are shown in Figure 1.

Figure 1: Markov Model Structure



Source: Sponsor's pharmacoeconomic report.[5]

Table 11: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Study CL301 for the pediatric subgroup (model initiation age: 1 years of age); Study CL303 for the adult subgroup (model initiation age: 39.9 years of age)[3,4]	The baseline patient characteristics were, for the most part, consistent with the study population, with the exception of the pediatric age (average age in Study CL301 = 6.27 years). Age was not a major driver in the pediatric model.
Efficacy and natural history	Pediatric model: Transition probabilities between low RSS and high RSS states were based on combined data from studies CL201, CL205, and CL301.[4,6,7] Transition probabilities for BSC were based on combined data from UK chart review and Study CL301.[4] After patients turned 18, transition probabilities for patients' transition between different fracture states were derived from Study CL303.[3]	Significant concerns exist regarding the comparative efficacy of patient-important outcomes in both the pediatric and adult phases of the models. See "Limitations of Sponsor's Submission" for details. Unclear whether patients in the placebo arm would reflect patients on BSC as modelled. See "Limitations of Sponsor's Submission" for details. Scenario analysis was conducted in which the comparator in the adult phase of the model reflected no treatment, which is in line with the trial comparator.

Data input	Description of data source	Comment
Utilities	Before age 18, utility inputs were based on the values reported in the NICE evaluation report, which were based on a sponsor-conducted utility study in which, using the EQ-5D-5L, vignettes describing the modelled health states were developed and valued by 6 clinicians with experience in treating XLH.[5] After age 18, the general XLH utility of 0.648 was considered for all patients based on Forestier-Zhang 2016.[13] Patient with fractures incurred an additional disutility of –0.108 in the incident year based on Kanis 2004.[14] Patients treated with burosumab would incur an additional QALY benefit of 0.044 each cycle, as measured by the reported change in WOMAC score in Study CL303 converted into an EQ-5D value.[9]	Inappropriate. See "Limitations of Sponsor's Submission" for details. Inappropriate. See "Limitations of Sponsor's Submission" for details.
Adverse events (indicate which specific adverse events were considered in the model)	NA	Acceptable, according to clinical experts consulted by CADTH, as most AEs were relatively minor.
Mortality	The model considered the normal population mortality based on the Canadian Life Tables before age 50.[29] Increased mortality risk was considered for patients with fractures after age 50, based on Klop 2017.[8]	See "Limitations of Sponsor's Submission" for details. Difference in mortality by fracture status from observational data from the general population may not hold true in this population and for this treatment. Interventional RCTs of fracture prevention demonstrate only a small difference in mortality.[20]
Discontinuation rate	Complete compliance with burosumab was considered until age 18. After age 18, treatment discontinuation was allowed for a fixed proportion of patients based on discontinuation data from Study CL303, which recurred over each cycle of the model. Patients who discontinued from burosumab were assumed to have the same efficacy and cost as the BSC arm.[5]	See "Limitations of Sponsor's Submission" for details. The CADTH clinical experts indicated that patients would require treatment in adulthood and would be unlikely to discontinue.
Event	Before age 18, surgeries (i.e., osteotomy, stapling of growth plates, and root canal) were assumed for patients in the high RSS state. The frequencies were estimated from Study CL201 root canals and from the sponsor-commissioned studies for other procedures.[5] After age 18, the types of surgeries included hip replacement, knee replacement, and root canal. For BSC, the	Uncertain, although unlikely to affect the model.

Data input	Description of data source	Comment
	frequencies were estimated from a sponsor-commissioned survey.[5]	
Resource use and costs		
Drug	Burosumab drug cost was calculated based on unit price,[2] frequency of use, average dose based on patient weight, and administration costs. BSC drug cost was calculated based on BSC unit price and frequency of use of oral phosphate and vitamin D. The unit price was obtained from the Ontario Drug Benefit Formulary[21] for vitamin D ± calcimimetic. After age 18, a fraction of patients was assumed to receive BSC based on reported baseline utilization from Study CL303 and a sponsor-conducted survey (of disease condition and quality of life) for calcimimetic.[5]	Likely appropriate.
Administration	Additional costs for subcutaneous administration were considered for burosumab, according to the Ontario Schedule of Benefits.[15]	Appropriate.
Event	Pain and mobility costs consisted of walking devices, physical therapy, and pain medication. The expected use of walking devices was informed by a sponsor-conducted survey.[5] Before age 18, patients in a low RSS state were assumed to have no mobility costs. Physical therapy and walking devices for children in a high RSS state was derived from expert opinion.[5] After age 18, burosumab was assumed to be associated with a 50% offset in mobility cost based on assumption, and an offset of up to 72% in pain medication cost based on Study CL303 observation. With the exception of root canal surgeries in children in the high RSS state (estimated from Study CL201), all other surgical costs were estimated from a sponsor-conducted survey. After age 18, burosumab was assumed to be associated with a 50% offset in surgical cost.[5] Fracture costs were obtained from a US study by Pike et al. (2010)[30] and were calculated as the difference in cost between	See “Limitations of Sponsor’s Submission” for details. The use of these are assumed and uncertain. However, these assumptions are unlikely to affect the model, as per the scenario analyses conducted by CADTH.

Data input	Description of data source	Comment
	the patient cohort with osteoporosis and fractures and a matched control cohort with osteoporosis and no fractures.	
Health state	Surveillance costs for burosumab were based on the monitoring recommendation as indicated in the burosumab label for the first 3 months. After 3 months, patients were assumed to follow the same monitoring frequency as those on BSC, except for serum and urinary lab measures, renal ultrasound, and radiography.[5] BSC surveillance was obtained from the treatment guidelines for patients with XLH and the NICE evaluation report.[12,16]	Uncertain. Scenario analyses found that monitoring costs were relatively small, and did not affect the model results.

AE = adverse event; BSC = best supportive care; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels; NA = not available; NICE = National Institute for Health Care and Excellence; QALY = quality-adjusted life-year; RCT = randomized controlled trial; RSS = Rickets Severity Score; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; XLH = X-linked hypophosphatemia.

Table 12: Sponsor's Key Assumptions

Assumption	Comment
Efficacy remains constant beyond the study follow-up time.	Uncertain.
Mortality benefit is achieved by preventing fracture in those over age 50.	Unknown. See "Limitations of Sponsor's Submission" for details. No mortality benefits were reported in comparative studies.

Sponsor's Results

Pediatric subgroup

Table 13: Summary of Results of the Sponsor's Base Case (Pediatric Subgroup)

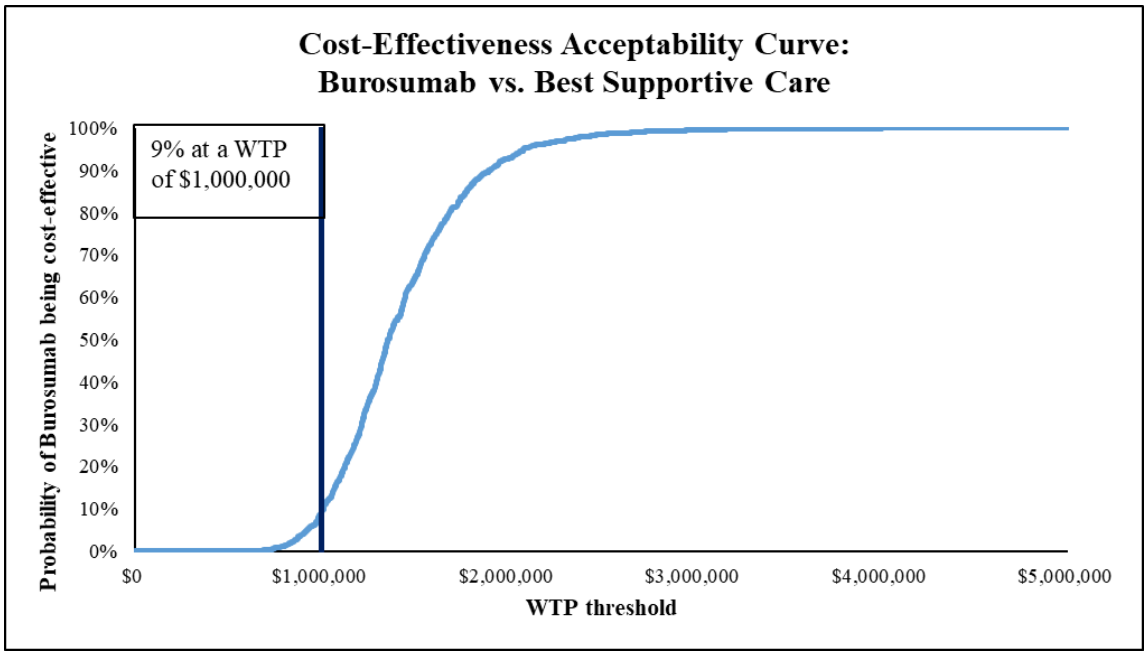
	Burosumab	BSC	Burosumab vs. BSC
Costs (2018)			
Total costs	**$9,031,119**	**$1,137,173**	**$7,893,946**
Drug and administration cost	$8,276,035	$29,944	$8,246,092
Surveillance cost	$16,822	$20,300	–$3,477
Fracture cost	$131,958	$345,056	–$213,098
Pain and mobility cost	$579,137	$703,256	–$124,119
Surgical cost	$18,378	$29,769	–$11,392
Terminal care cost	$8,789	$8,848	–$59
Outcomes			
LYs	**46.39**	**46.26**	**0.13**
QALYs	**32.07**	**26.29**	**5.78**
Incremental cost-effectiveness ratios			
Incremental cost per LY gained ($/LY)			**$59,272,605**

	Burosumab	BSC	Burosumab vs. BSC
Incremental cost per QALY gained ($/QALY)			**$1,364,863**

BSC = best supportive care; LY = life-year; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[5]

Figure 2: Cost-Effectiveness Acceptability Curve (Pediatric Subgroup)



WTP = willingness-to-pay; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[5]

Adult Subgroup

Table 14: Summary of Results of the Sponsor's Base Case (Adult Subgroup)

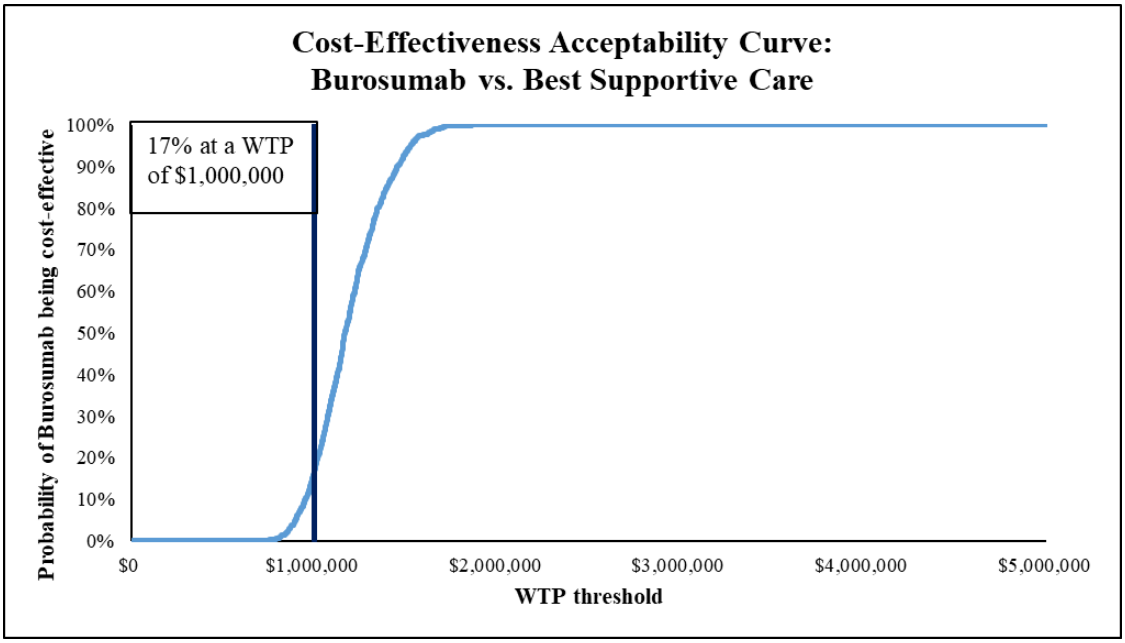
	Burosumab	BSC	Burosumab vs. BSC
Costs (2018)			
Total costs	**$4,628,086**	**$1,053,297**	**$3,574,790**
Drug and administration cost	$3,932,740	$12,220	$3,920,520
Surveillance cost	$11,851	$12,662	–$811
Fracture cost	$108,390	$312,032	–$203,642
Pain and mobility cost	$543,212	$681,422	–$138,210
Surgical cost	$16,739	$19,536	–$2,798
Terminal care cost	$15,154	$15,425	–$271
Outcomes			
LYs	**31.04**	**30.44**	**0.60**
QALYs	**19.68**	**16.49**	**3.19**

	Burosumab	BSC	Burosumab vs. BSC
Incremental cost-effectiveness ratios			
Incremental cost per LY gained ($/LY)			**$5,959,766**
Incremental cost per QALY gained ($/QALY)			**$1,119,456**

BSC = best supportive care; LY = life-year; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[5]

Figure 3: Cost-Effectiveness Acceptability Curve (Adult Subgroup)



WTP = willingness-to-pay; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[5]

Table 15: Summary of Results of the Sponsor's Base Case (Subgroup Analysis of Adult Patients With History of Fracture)

	Crysvita	BSC	Crysvita vs. BSC
Costs (2018)			
Total costs	**$5,252,334**	**$1,280,982**	**$3,971,352**
Drug and administration cost	$4,484,020	$12,179	$4,471,842
Surveillance cost	$11,191	$11,760	–$570
Fracture cost	$217,441	$589,961	–$372,519
Pain and mobility cost	$508,043	$632,513	–$124,469
Surgical cost	$15,721	$18,134	–$2,413
Terminal care cost	$15,917	$16,435	–$518
Outcomes			
LYs	**29.42**	**28.25**	**1.17**
QALYs	**17.79**	**12.14**	**5.65**

	Crysvita	BSC	Crysvita vs. BSC
Incremental cost-effectiveness ratios			
Incremental cost per LY gained ($/LY)			**$3,406,470**
Incremental cost per QALY gained ($/QALY)			**$702,672**

BSC = best supportive care; LY = life-year; QALY = quality-adjusted life-year; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[5]

CADTH Reanalyses

Table 16: CADTH Reanalysis (Deterministic Results)

	Total costs ($)	Total LYs	Total QALYs	Inc. cost ($)	Inc. LYs	Inc. QALYs	Inc. cost per LY ($)	ICER ($/QALY)
Pediatric subgroup								
BSC	1,165,990	46.76	26.73					
Burosumab	17,077,797	46.85	32.73	15,911,807	0.10	6.01	166,305,926	2,651,574
Adult subgroup								
BSC	1,114,927	31.39	16.82					
Burosumab	12,248,068	31.58	20.07	11,133,140	0.19	3.25	58,691,360	3,426,584

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LY = life-year; QALY = quality-adjusted life-year.

Note: The sponsor's model does not report probabilistic results of the total expected values.

Table 17: Scenario Analyses of the CADTH Base Case

Description	Burosumab vs. BSC		
	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
Pediatric subgroup			
CADTH base case (pediatric)	**16,238,620**	**6.01**	**2,703,146**
0% in low RSS state (i.e., all patients initiating at high RSS state)	16,238,433	6.04	2,688,190
Omits dental and assistive device costs	16,241,809	6.01	2,703,677
Same probability of developing new fractures in both treatment arms	16,265,975	5.65	2,881,097
Fracture-related mortality (SMR = 1)	16,237,714	5.98	2,717,333
Same mobility and surgical cost as BSC	16,257,859	6.01	2,706,348
Same surveillance cost	16,243,349	6.01	2,703,933
No discontinuation	17,037,503	5.99	2,846,479
Set BSC cost to $0 after aged 18	16,250,538	6.01	2,705,130
Adult subgroup			
CADTH base case (adult)	**11,465,179**	**3.25**	**3,523,922**
Adult subgroup with prior history of fracture	11,140,480	6.89	1,618,065
Omits dental and assistive device costs	11,468,352	3.25	3,524,898
Same probability of developing new fractures in both treatment arms	11,492,957	2.87	4,000,222
Fracture-related mortality (SMR = 1)	11,460,832	3.20	3,578,636

Description	Burosumab vs. BSC		
	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
Same mobility and surgical cost as BSC	11,484,769	3.25	3,529,944
Same surveillance cost	11,468,389	3.25	3,524,909
No discontinuation	11,878,272	3.25	3,658,575
Set BSC cost to $0 after age 18 years	11,477,277	3.25	3,527,641
Adult subgroup with prior history of fracture	11,140,480	6.89	1,618,065

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RSS = Rickets Severity Score; SMR = standardized mortality ratio; vs. = versus.

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