CADTH

CADTH COMMON DRUG REVIEW

Clinical 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.

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	July 2020
Report Length:	197 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Tables

Figures

Abbreviations

1,25(OH)$_2$D	1,25-dihydroxyvitamin D
6MWT	6-minute walk test
AE	adverse event
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
BALP	bone-specific alkaline phosphatase
BFI	Brief Fatigue Inventory
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency – Second Edition
BPI	Brief Pain Inventory
CALIPER	Canadian Laboratory Initiative on Paediatric Reference Intervals
CAT	computerized adaptive test
CI	confidence interval
CORD	Canadian Organization for Rare Disorders
CTx	carboxy terminal cross-linked telopeptide of type 1 collagen
FAS	full analysis set
FGF23	fibroblast growth factor 23
FPS	Faces Pain Scale
FPS-R	Faces Pain Scale – Revised
GEE	generalized estimating equation
HRQoL	health-related quality of life
ISR	injection-site reaction
ITT	intention to treat
LLN	lower limit of normal
LS	least squares
MCID	minimal clinically important difference
O.Th	osteoid thickness
OV/BV	osteoid volume/bone volume
P1NP	procollagen type 1 N-propeptide
PAS	primary analysis set
PHEX	phosphate-regulating endopeptidase homolog, X-linked
PHS	Physical Summary Score
PODCI	Pediatric Outcomes Data Collection Instrument
POSNA	Pediatric Orthopaedic Society of North America
PROMIS	Patient-Reported Outcomes Measurement Information System
PSS	Psychosocial Summary Score
PTH	parathyroid hormone

RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Score
SAE	serious adverse event
SAS	safety analysis set
SC	subcutaneous
SD	standard deviation
SE	standard error
SF-10	Short Form (10) Health Survey for Children
TEAE	treatment-emergent adverse event
TmP/GFR	ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate
TRP	tubular reabsorption of phosphate
ULN	upper limit of normal
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
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) and route of administration) and strength(s)	10 mg/mL, 20 mg/mL, and 30 mg/mL single-use 1 mL vials
NOC date	December 5, 2018
Manufacturer	Kyowa Kirin Limited

Executive Summary

Introduction

X-linked hypophosphatemia (XLH) is a rare, genetic, chronically debilitating disorder of phosphate homeostasis that leads to defective bone mineralization. It manifests as rickets in children and osteomalacia in children and adults.[1-4] Patients with XLH have elevated levels of fibroblast growth factor 23 (FGF23). Excess FGF23 suppresses proximal renal tubular reabsorption of phosphate (TRP), leading to phosphaturia, and inhibits the renal production of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), resulting in decreased intestinal absorption of calcium and phosphate.[1-4] Currently, treatment of XLH in children involves phosphate supplementation (usually through multiple daily doses of oral phosphate salts) and vitamin D supplementation with active vitamin D analogues. In adults, primary treatment generally consists of continued use of oral phosphate and active vitamin D analogues as well as pain management and orthopedic interventions.[1,3] As is the case with many rare diseases, 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.[5] The estimated prevalence of hypophosphatemic rickets in southern Denmark is 4.8 per 100,000 persons (children and adults).[6] There are no known reported prevalence estimates for Canada.

Burosumab is indicated for the treatment of XLH in adult and pediatric patients one year of age and older.[7] The Health Canada–recommended starting dose of burosumab in pediatric patients with XLH (one year to less than 18 years of age) is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered by subcutaneous (SC) injection every two weeks. The minimum starting dose is 10 mg; the maximum dose is 90 mg. The Health Canada–recommended starting dose of burosumab in adult patients with XLH (18 years of age and older) is 1 mg/kg of body weight rounded to the nearest 10 mg, administered by SC injection every four weeks; the maximum dose is 90 mg. Burosumab should not be administered at doses greater than 1 mg/kg (more than 90 mg) in adults. In both pediatric and adult patients, the dose may be adjusted based on serum phosphorus levels.[7]

The objective of this CADTH Common Drug Review is to perform a systematic review of the beneficial and harmful effects of burosumab for the treatment of XLH in adult and pediatric patients one year of age and older.

Stakeholder Engagement

Patient Input

With support from the XLH Network, one patient group, the Canadian Organization for Rare Disorders (CORD), provided patient input for this submission. Information was collected primarily through online surveys and individual interviews with patients and parents who had experience with Crysvita.

Patients indicated that symptoms of XLH include chronic debilitating pain, bone and joint deformities in legs and spine, severe dental problems, fractures, stiffness, short stature, hearing problems, and osteoarthritis with aging. Treatments (surgeries and medication regimes) for XLH were associated with significant social, educational, or work challenges, financial difficulties, and psychological impacts on patients and their families. For older adults, the physical symptoms (bone and joint damage) accumulate, as do the psychological impacts. All these have serious deleterious impacts on quality of life for patients and their families.

Patients indicated that existing therapies (prior to burosumab) had, at best, only moderate benefits in addressing symptoms or reducing disease progression, with many feeling the impacts were limited or very limited. This was expressed by patients (and caregivers) of all ages, although the impact of the disease was progressive and older adults were considerably less mobile, less engaged, and more depressed.

Clinician Input[1]

The clinical experts indicated that while in pediatric patients, growth, limb deformities, joint pain, and quality of life may improve with conventional therapy of oral phosphate supplements and active vitamin D analogues, the treatment seldom normalizes the phosphate levels and the mineralization of bones; nor does it prevent the long-term skeletal complications of XLH, such as dental disease, bony deformities, arthritic complications, and enthesopathy or spinous ligament calcification. In adult patients, osteoarthritis and enthesopathies are not generally addressed by current conventional therapies. Furthermore, the frequency of the required administration of phosphate and calcitriol often results in poor compliance across all ages, because phosphate treatment needs to be administered anywhere from two to six times per 24-hour period, while calcitriol needs to be administered one or two times per 24-hour period.

The clinical experts indicated that as a result, it is anticipated that burosumab would replace conventional therapies and significantly shift the current treatment paradigm. Given that burosumab is expensive and relatively new, and because long-term safety and efficacy data for burosumab are lacking, the clinical experts thought that for patients who are younger than one year of age, have mild disease, are pregnant or breastfeeding, or suffer from severe renal impairment or end-stage renal disease, it would be appropriate to try the conventional therapy of oral phosphate supplements and active vitamin D analogues first, then switch to burosumab if complications arise. However, for patients with severe disease, the clinical experts expected that burosumab would be used as the first-line treatment.

[1] This information is based on information provided in draft form by clinical experts consulted by CADTH Common Drug Review for the purpose of this review.

Only a small number of studies were available, and all clinical trials enrolled only a small number of patients. All clinical experts indicated that if more evidence become available, and if the cost of burosumab was not an issue, then they would prescribe burosumab for all patients as the first-line treatment regardless of severity, except in the case of infants and pregnant or breastfeeding women.

The clinical experts indicated that the pediatric and adult patients best suited for treatment with burosumab are symptomatic and have: reduced serum phosphate and $1,25(OH)_2D$ levels; confirmed mutation of the phosphate-regulating endopeptidase homolog, X-linked (PHEX) in the patient or in a directly related family member with appropriate X-linked inheritance; and elevated FGF23 levels. In addition, the panel indicated that pediatric patients should have a Rickets Severity Score (RSS) of at least 2. Nevertheless, it may be difficult to determine a set of distinct characteristics for pediatric patients who would best respond to treatment with burosumab, given the limited data available. In addition, pediatric patients who have mild disease (defined by the clinical experts as an RSS of less than 2) should not receive burosumab treatment. Nevertheless, these pediatric patients would need to be monitored and started on conventional therapy if required; if they experienced a decline in growth velocity, or any progression of deformity after receiving conventional therapy, they should be switched to burosumab. The approach to treating adult patients varied among panel members. In one approach, burosumab treatment would be initiated only in those with severe manifestations (i.e., who have nephrocalcinosis, poor mobility, significant bone and joint pain, hyperparathyroidism, or radiographic evidence of osteomalacia with fractures or pseudofractures). In another approach, all adult patients with documented XLH would initially receive burosumab regardless of severity. However, it was agreed that patients who have the most severe manifestations would likely respond best to treatment with burosumab.

The clinical experts indicated that a pediatric patient is considered a responder if the phosphate levels are normalized, $1,25(OH)_2D$ levels are improved, and there is improved linear growth and healing of rickets. Radiographic X-rays would be conducted one year after the initiation of burosumab treatment, while biochemical evaluation would be conducted every four to six months. The panel indicated that treatment response should be assessed yearly for renewal purposes. For adult patients, meaningful responses to treatment include decreased bone pain, increased mobility, prevention and healing of fractures and pseudofractures (radiologically documented), and prevention of dental abscesses. Biochemical evaluation would be conducted every four to six months; once patients are stable on burosumab, biochemical evaluation could be conducted once a year. Radiographic assessment would also be conducted once a year. The panel indicated that the treatment response should be assessed yearly for renewal purposes.

Treatment discontinuation should be considered in cases of lack of response — e.g., due to development of neutralizing antibodies — or in cases where unacceptable side effects are present, such as severe cutaneous reactions.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

A total of four studies met the inclusion criteria for this review: three in children (Study CL301, Study CL201, and Study CL205) and one in adults (Study CL303).

Study CL301 (N = 61) was a multi-centre, randomized, open-label, phase III study comparing the efficacy and safety of burosumab to active control (oral phosphate and active vitamin D therapy) in children (one year to ≤ 12 years of age) with XLH. Eligible patients were randomized in a 1:1 ratio to receive either open-label burosumab (administered by SC injection) every two weeks or phosphate and active vitamin D therapy (administered orally) daily for a total of 64 weeks. Patients randomized to the burosumab treatment group received burosumab at a starting dose of 0.8 mg/kg every two weeks. The dose could be titrated to 1.2 mg/kg every two weeks based on fasting serum phosphorus concentrations. The maximum allowable dose of burosumab per administration was 90 mg. For patients randomized to the active-control treatment group, the dose of oral phosphate and active vitamin D therapy was administered on an individualized basis at the discretion of the investigator. Calcitriol and alfacalcidol dosages were adjusted based on the clinical and laboratory values that guide best possible treatment.

Study CL201 (N = 52) was a randomized, multi-centre, open-label, dose-finding, phase II study to assess the efficacy and safety of burosumab in children (five years to 12 years old) with XLH. Patients were randomized 1:1 to burosumab every two weeks or every four weeks for a total of 64 weeks. (Consistent with the frequency in the approved product monograph, only results for every two-week arm are reported in this summary, as shown in Table 1.) This was followed by a long-term extension phase, during which patients in the every-four-weeks arm shifted to receive burosumab every two weeks at 60% of the dose administered every four weeks (rounded to the nearest 10 mg). For patients randomized to burosumab every two weeks, the initial doses were 0.1 mg/kg, 0.2 mg/kg, or 0.3 mg/kg every two weeks, subsequently adjusted every four weeks in 0.3 mg/kg increments, as needed, based on two-week, post-dose (peak) fasting serum phosphorus levels.

Study CL205 (N = 13) was a multi-centre, open-label, single-arm, phase II study in children (ages one year to four years) with XLH who were treatment-naive or had previously received standard therapy with oral phosphate and active vitamin D. Study CL205 assessed the safety and efficacy of burosumab administered through SC injections every two weeks for a total of 64 weeks. Patients who were receiving oral phosphate and active vitamin D therapy discontinued treatment during screening and for the duration of the study. All patients received burosumab at a starting dose of 0.8 mg/kg every two weeks, which could be titrated to 1.2 mg/kg every two weeks at any time during the study if a patient met the dose-adjustment criteria. Results were only available until week 40.

Study CL303 (N = 134) was a randomized, double-blind, placebo-controlled, multi-centre, phase III study that evaluated the efficacy and safety of burosumab in adults (18 years to 65 years of age) with XLH. Patients were randomized in a 1:1 ratio to receive burosumab or placebo every four weeks for a total of 24 weeks followed by a long-term extension phase during which patients in the placebo arm shifted to receive burosumab at the same dosage as in the active treatment arm. Patients randomized to the burosumab treatment group received burosumab 1 mg/kg (rounded to the nearest 10 mg) with a maximum allowable dose of 90 mg.

Studies CL301, CL201 (and its long-term extension), and CL205 assessed treatment effect with two radiographic scoring methods and their individual components: the RSS and the Radiographic Global Impression of Change (RGI-C) scale. The RSS is a 10-point scale constructed to measure rickets severity in the wrists and knees based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected. The RGI-C scale is a 7-point scale that, as a complement to RSS, assesses the change in bone

structure associated with the pathophysiology of hypophosphatasia. Other related outcome measures included the 6-minute walk test (6MWT) in studies CL301 and CL303; assessment of pain using the Faces Pain Scale – Revised (FPS-R) in Study CL301; the Brief Pain Inventory (BPI) in Study CL303; health-related quality of life (HRQoL), evaluated using the Short Form (10) Health Survey for Children (SF-10) in Study CL301; stiffness and physical function assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire in Study CL303; and serum phosphorus concentration in all of the included studies.

It is worth noting that while the use of the RSS and RGI-C was deemed adequate to demonstrate clinical efficacy in children by Health Canada reviewers,[8] no minimal clinically important difference (MCID) for the RSS or RGI-C was identified for patients with XLH; therefore, the clinical importance of improvement in these outcomes is unknown. In addition, these tools lack fully independent validation.

The primary outcome in Study CL301 was change from baseline in rickets at week 40 as assessed by the RGI-C global score. Secondary outcomes included RSS total score, RSS knee and wrist scores at week 40 and week 64, RGI-C global score at week 64, growth velocity, and serum phosphorus concentration.

The primary outcome in Study CL201 was change from baseline in severity of rickets as measured by RSS total score. Secondary outcomes included RSS knee and wrist scores, RGI-C global, knee, wrist, and long leg scores, and serum phosphorus concentration.

The primary outcome in Study CL205 was change from baseline in serum phosphorus at week 40. Secondary outcomes included RGI-C global score, RGI-C wrist and knee scores, RSS total score, RSS wrist and knee scores, and recumbent length or standing height.

The primary outcome in Study CL303 was the proportion of patients achieving mean serum phosphorus levels above the lower limit of normal (LLN). Secondary outcomes included assessments of pain, fatigue, stiffness, and physical function.

Efficacy Results

The mean baseline values for RSS were quite different among studies CL301 (3.18), CL201 (1.92), and CL205 (2.92), indicating a significantly different severity of rickets in the pediatric populations included in these studies. A higher RSS total score indicates more severe rickets, while an RSS of 1.5 is perceived to be quite mild.

In Study CL301, assessments using the RSS method showed greater reductions in rickets severity with burosumab treatment. The mean RSS total score decreased in the burosumab group from 3.17 at baseline to 1.13 at week 40, as compared with a decrease in the active-control group from 3.19 to 2.47. This reduction was maintained at week 64. The difference in RSS total score for change from baseline at week 40 was statistically significant at −1.34 (95% confidence interval [CI], −1.74 to −0.94; P < 0.0001); at week 64 it was −1.21 (95% CI, −1.59 to −0.83; P < 0.0001). Similar decreases in rickets severity were observed for mean RSS knee scores and mean RSS wrist scores at both week 40 and week 64.

The other two studies of pediatric patients (studies CL201 and CL205) had no active comparator arms. Despite notable difference in baseline severity (RSS total scores of 1.92 and 2.92 in studies CL201 and CL205, respectively), pediatric patients who received burosumab every two weeks showed consistent improvements, as demonstrated by within-group changes from baseline to week 40 in RSS total score (−1.0695% [95% CI, −1.28 to

−0.85; P < 0.0001] in Study CL201 and −1.73 [95% CI, −2.03 to −1.44; P < 0.0001] in Study CL205). In Study CL301, the within-group change from baseline to week 40 in RSS total score was −2.04.

In Study CL301, least squares (LS) mean RGI-C global scores at week 40 were 1.92 in the burosumab group and 0.77 in the active-control group, a statistically significant difference of 1.14 (95% CI, 0.83 to 1.45; P < 0.0001); this improvement was maintained at week 64 with a score of 1.02 (95% CI, 0.72 to 1.33; P < 0.0001). Greater healing in the burosumab group compared with the active-control group was also observed in RGI-C knee and wrist scores at both week 40 and week 64. Burosumab treatment resulted in substantial healing of rickets (defined as an RGI-C global score ≥ +2.0) in 72% of patients at week 40 compared with 6% of patients treated with active control; this difference was maintained at week 64. Lower extremity skeletal abnormalities, assessed by RGI-C in standing long leg radiographs, also showed greater healing in the burosumab group compared with the active-control group. At week 64, LS mean RGI-C lower limb deformity scores were 1.25 in the burosumab group and 0.29 in the active-control group, a mean difference of 0.97 (95% CI, 0.57 to 1.37; P < 0.0001). However, an MCID for the RSS or RGI-C was not identified for patients with XLH; therefore, the clinical importance of the improvement in these outcomes is unknown.

In Study CL301, differences in RGI-C global scores and RSS total scores between the treatment groups were analyzed in subgroups of baseline rickets severity (RSS total score ≤ 2.5 versus > 2.5) and age (less than five years versus greater than or equal to five years old). The results in the subgroups were similar to those of the overall study population.

In Study CL301, of the 29 patients randomized to the burosumab treatment group, 17 patients (58.6%) and 19 patients (65.5%) had serum phosphorus concentrations within the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40 and at week 64, respectively. Of the 32 patients randomized to the active-control group (oral phosphate and active vitamin D therapy), only one patient (3.1%) had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40 and week 64. In the subgroup of patients younger than five years of age, nine patients (64.3%) in the burosumab treatment group had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) versus none in the active-control group. In the subgroup of patients five years of age and older, eight patients (53.3%) in the burosumab treatment group had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) versus one patient (5.0%) in the active-control group. No statistical comparison between the two treatment groups was conducted. It is worth noting that no reference was provided for the normal range of serum phosphorus (1.03 mmol/L to 1.97 mmol/L) used in Study CL301. The clinical experts consulted for this review indicated that they use the numbers provided in the Canadian Laboratory Initiative on Paediatric Reference Intervals (CALIPER) database,[9] which provides biochemical markers across the pediatric age span (birth to 18 years). This database indicates that the normal range of serum phosphorus for the age group one year to less than five years of age is higher than the range for the age group five years to less than 13 years of age. In addition, none of the measures reported in the CALIPER database[9] had the lower bound for the age group one year to less than five years, at 1.03 mmol/L (the lowest reported is 1.26 mmol/L). The sponsor clarified that the serum phosphorus levels were determined according to the standards in place in local laboratories. However, the normal range of serum phosphorus used was the same regardless of age; hence, there is uncertainty around the number of patients who actually

achieved the normal range of serum phosphorus for patients younger than five years of age.

Study CL303 was the only study with a relatively large sample size (N = 134) that studied adult patients. It demonstrated a statistically significant effect of burosumab relative to placebo in increasing serum phosphorus concentrations from baseline to week 24, with a total of 94.1% of patients in the burosumab group achieving a mean serum phosphorus concentration above the LLN (0.81 mmol/L) across the midpoints of the dose intervals through week 24, compared with only 7.6% of patients in the placebo group (P < 0.0001).

Mobility in the CL301 study was assessed using the 6MWT and the Patient-Reported Outcomes Measurement Information System (PROMIS) score for physical function mobility scales in patients aged greater than or equal to five years. The difference in 6MWT between the treatment groups for the change from baseline to week 40 was 43 m (95% CI, −0.3 to 87; P = 0.0514), which was not statistically significantly different; at week 64, it was 46 m (95% CI, 2 to 89; P = 0.0399) in favour of burosumab. The difference between treatment groups exceeds the MCIDs established for patients with hypophosphatasia (31 m for children and adults; 43 m for adolescents). On the other hand, the PROMIS score for the physical function mobility scales did not show statistically significant differences between the treatment groups, where the change from baseline was 2.68 at week 40 (95% CI, −0.52 to 5.89; P = 0.1009) and 1.90 at week 64 (95% CI, −1.80 to 5.59; P = 0.3145).

Mobility in the CL303 study was assessed using the 6MWT and WOMAC physical function. The difference in the 6MWT between treatment groups for the change from baseline to week 24 was 19.93 m (95% CI, 4 to 36; P = 0.0120) in favour of burosumab; however, this difference may not be clinically relevant, given that it did not exceed the established MCID of 31 m for patients with hypophosphatasia. Also, while WOMAC physical function impairment favoured burosumab, the differences between the burosumab and placebo groups at week 24 were not statistically significant after multiplicity adjustment.

Pain in the CL301 study was assessed using the FPS-R and PROMIS pain interference in patients who were at least five years of age. There was no notable change between treatment groups for the FPS-R (P = 0.9905 at week 4 and P = 0.8786 at week 64). While PROMIS pain interference t scores indicated more reduction in pain in the burosumab treatment group than in the active-control group at week 40, at −5.02 (95% CI, −9.29 to −0.75; P = 0.0212), the difference between the treatment groups was smaller at week 64, at −2.26 (95% CI, −6.61 to 2.09; P = 0.3091). While these results indicate that burosumab might not have benefit in terms of pain, it is worth noting that for these outcomes, only 15 patients were included in the burosumab group and 20 patients were included in the active-control group.

In the CL303 study, WOMAC stiffness and BPI were used to assess pain and stiffness. While the burosumab group had a statistically significant decrease from baseline in WOMAC stiffness scores relative to the placebo group at week 24 (the LS mean difference between treatment groups at week 24 was −8.31 [95% CI, −14.68 to −1.94; P = 0.0106]), there is no MCID established for this scale; therefore, the clinical importance of these improvements is unknown. Results for BPI worst pain did not show statistically significant differences between burosumab and placebo groups at week 24 after multiplicity adjustment (the LS mean difference between treatment groups at week 24 was −0.46 [95% CI, −1.00 to 0.08; P = 0.0919]). In addition, the BPI pain severity and the BPI pain interference scores did not show differences between the burosumab and placebo treatment groups. For BPI pain severity, the LS mean difference between treatment groups

at week 24 was −0.43 (95% CI, −0.93 to 0.07; P = 0.0926); for BPI pain interference, the LS mean difference between treatment groups at week 24 was −0.13 (95% CI, −0.70 to 0.44; P = 0.6511). The clinical experts indicated that the duration of the study (24 weeks) might have been too short to notice any improvement in pain, and that the lack of patient-reported improvements in physical function or pain were likely to reflect the multifactorial nature of XLH presentation in adults.

Fatigue was assessed using the PROMIS fatigue t score in Study CL301 and the Brief Fatigue Inventory (BFI) in Study CL303. In Study CL301, no difference between the burosumab group and the active-control group was found in fatigue t score. Similarly, no difference between the burosumab and placebo groups was reported in Study CL303 for the BFI worst fatigue score and for the BFI global fatigue score. For the BFI worst fatigue score, the LS mean difference between treatment groups at week 24 was −0.20 (95% CI, −0.80 to 0.40; P = 0.5150); for the BFI global fatigue score, the LS mean difference between treatment groups at week 24 was 0.11 (95% CI, −0.46 to 0.67; P = 0.7129).

HRQoL measures were included in this systematic review to provide a patient perspective on treatment with burosumab. The SF-10 physical summary score (PHS) and psychosocial summary score (PSS) were exploratory efficacy end points in the CL301 study, and no statistical significance test for comparison between the two treatment groups was conducted. Therefore, no statistical inference could be drawn regarding whether burosumab improved HRQoL compared to phosphate and active vitamin D therapy.

Fractures and pseudofractures were also considered important outcomes to patients, as reported in the patient input section. At week 24, 50% of patients (16 out of 32) in the burosumab group had full healing of at least one active fracture or pseudofracture compared with 13% of patients (five out of 38) in the placebo group. However, the presence of pseudofractures and fractures appeared to have no relationship to pain scores at baseline. In addition, an FDA analysis suggested that radiographic healing was not a strong predictor of relief from pain.[2] Therefore, the clinical significance of improved fracture healing was somewhat unclear with regard to alleviation of pain, but was not inconsistent with the view that pain in XLH is multifactorial and arises from a combination of long-standing disease manifestations (enthesopathy) as well as potentially treatable elements (osteomalacia and fractures and/or pseudofractures).

Harms Results

The overall frequency of treatment-emergent adverse events (TEAEs) was similar between studies for those who received burosumab: adverse events (AEs) were reported by all patients who received burosumab in studies CL301, CL201, and CL205 and by 94.1% of patients who received burosumab in Study CL303. In Study CL301, 84% of patients (27 out of 32) in the active-control group experienced at least one TEAE. In the CL303 study, 92.4% of patients (61 out of 66) in the placebo group experienced at least one TEAE.

The safety profile did not raise any serious concerns. The number of serious adverse events (SAEs) was low in all of the included studies. No patient withdrew from treatment or from the studies for AEs, and no deaths were reported during the studies. In Study CL301, 15 patients in the burosumab group (52%) experienced injection-site reactions (ISRs). Hypersensitivity TEAEs were experienced by 11 patients (38%) in the burosumab group and six patients (19%) in the active-control group. No TEAEs of hyperphosphatemia, ectopic mineralization, or restless leg syndrome were reported in either treatment group. In Study CL303, eight patients (11.8%) in the burosumab group and eight patients (12.1%) in

the placebo group experienced TEAEs of ISRs. Hypersensitivity was reported by four patients (burosumab: 5.9%; placebo: 6.1%) in each treatment group. TEAEs of hyperphosphatemia were reported by four patients (5.9%) in the burosumab group and by no patients in the placebo group. A total of eight patients (11.8%) in the burosumab group and five patients (7.6%) in the placebo group had a TEAE of restless leg syndrome or limb discomfort (13.5%). No TEAEs of ectopic mineralization were reported in either treatment group during the double-blind period. In studies CL301 and CL303, most of the AEs of special interest were considered mild or moderate, and none led to discontinuation of the study drug.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks	Placebo
RSS total score						
Baseline – mean (SD)	3.17 (0.975)	3.19 (1.141)	1.92 (1.172)	2.92 (1.367)	NA	NA
Change from baseline to week 40 – LS mean (95% CI)	−2.04 (−2.33 to −1.75)	−0.71 (−0.98 to −0.43)	−1.06 (−1.28 to −0.85)	−1.73 (−2.03 to −1.44)	NA	NA
Treatment-group difference versus control (95% CI) at week 40	−1.34 (−1.74 to −0.94)		NA	NA	NA	NA
P value	< 0.0001[a]		< 0.0001	< 0.0001[a]	NA	NA
Change from baseline to week 64 – LS mean (95% CI)	−2.23 (−2.46 to −2.00)	−1.01 (−1.31 to −0.72)	−1.00 (−1.22 to −0.79)	NR	NA	NA
Treatment-group difference versus control (95% CI) at week 64	−1.21 (−1.59 to −0.83)		NA	NR	NA	NA
P value	< 0.0001[a]		< 0.0001	NR	NA	NA
Proportion of patients achieving reduction from baseline at least 1.0 at week 64, n/N (%)	29/29 (100)	16/32 (50)	14/20 (70.0)	NR	NA	NA
Proportion of patients who healed completely (RSS = 0) at week 64, n/N (%)	4/29 (13.8)	0/32 (0)	6/25 (24.0)	NR	NA	NA
RGI-C global score						
Week 40 – LS mean (95% CI)	1.92 (1.70 to 2.14)	0.77 (0.56 to 0.99)	1.66 (1.48 to 1.84)	2.33 (2.16 to 2.51)	NA	NA
Treatment-group difference versus control (95% CI) at week 40	1.14 (0.83 to 1.45)		NA	NA	NA	NA
P value	< 0.0001		< 0.0001[a]	< 0.0001[a]	NA	NA
Week 64 – LS mean (95% CI)	2.06 (1.91 to 2.20)	1.03 (0.77 to 1.30)	1.56 (1.34 to 1.78)	NR	NA	NA

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks	Placebo
Treatment-group difference versus control (95% CI) at week 40	1.02 (0.72 to 1.33)		NA	NA	NA	NA
P value	< 0.0001[a]		< 0.0001[a]	NR	NA	NA
RGI-C responders (RGI-C global scores ≥ +2.0) at week 40	21 (72.4)	2 (6.3)	18/26 (69.2)	13 (100)	NA	NA
P value	< 0.0001[a]		NA	NA	NA	NA
RGI-C responders (RGI-C global scores ≥ +2.0) at week 64	25 (86.2)	6 (18.8)	15/26 (57.7)	NR	NA	NA
P value	0.0002[a]		NA	NA	NA	NA
Serum phosphorus concentration (mmol/L)						
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40, n (%)	17 (58.6)	1 (3.1)	17 (65.4)	10 (76.9)	NA	NA
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 64, n (%)	19 (65.5)	1 (3.1)	16 (66.7)	NR	NA	NA
Patients achieving mean serum phosphorus > LLN across midpoints of dose intervals through week 24 – n (%)	NR	NR	NR	NR	64 (94.1)	5 (7.6)
95% CI	NR	NR	NR	NR	(85.8 to 97.7)	(3.3 to 16.5)
P value	NR	NR	NR	NR	< 0.0001[b]	
Worst pain, by BPI						
LS mean (95% CI) change from baseline at week 24	NR	NR	NR	NR	−0.79 (−1.20 to −0.37)	−0.32 (−0.76 to 0.11)
Treatment-group difference versus control (95% CI) at week 24	NR	NR	NR	NR	−0.46 (−1.00 to 0.08)	
P value	NR	NR	NR	NR	0.0919[c]	
Physical functioning, by WOMAC						
LS mean (95% CI) change from baseline at week 24	NR	NR	NR	NR	−3.11 (−8.12 to 1.89)	1.79 (−3.54 to 7.13)
Treatment-group difference versus control (95% CI) at week 24	NR	NR	NR	NR	−4.90 (−9.76 to −0.05)	
P value	NR	NR	NR	NR	0.0478[d]	

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks	Placebo
Stiffness, by WOMAC						
LS mean (95% CI) change from baseline at week 24	NR	NR	NR	NR	−7.85 (−13.80 to −1.91)	0.46 (−5.70 to 6.61)
Treatment-group difference versus control (95% CI) at week 24	NR	NR	NR	NR	−8.31 (−14.68 to −1.94)	
P value	NR	NR	NR	NR	0.0106[e]	
SF-10 – physical summary score						
Baseline - n	15	20	26	NR	NR	NR
Mean (SD)	40.03 (10.07)	40.74 (15.30)	41.572 (12.1365)	NR	NR	NR
Week 64 – change from baseline, mean (SD)	6.08 (8.47)	0.33 (10.81)	5.834 (12.8870)	NR	NR	NR
P value	NR	NR	NR	NR	NR	NR
SF-10 – psychosocial summary score						
Baseline - n	15	20	26	NR	NR	NR
Mean (SD)	50.76 (9.65)	52.79 (9.40)	53.37 (9.52)	NR	NR	NR
Week 64 – change from baseline, mean (SD)	1.31 (8.18)	1.16 (6.24)	−0.52 (7.80)	NR	NR	NR
P value	NR		NR	NR	NR	NR
6MWT (m walked)						
Baseline – mean (SD)	385 (86)	451 (106)	480 (85)	NR	360 (110)	367 (104)
Change from baseline to week 40 – LS mean (95% CI)	47 (16 to 78)	4 (−24 to 31)	NR	NR	At week 24: 17 (3 to 32)	At week 24: −3 (−18 to 12)
Treatment-group difference versus control (95% CI) at week 40	43 (−0.3 to 87)		NA	NA	At week 24: 20 (4 to 36)	
P value	0.0514		NR	NR	At week 24: 0.0120	
Change from baseline to week 64 – LS mean (95% CI)	75 (50 to 99)	29 (−4 to 62)	+53 (35 to 70)	NR	NA	NA
Treatment-group difference versus control (95% CI) at week 64	46 (2 to 89)		NA	NA	NA	
P value	0.0399		< 0.0001	NR	NA	
SAEs						
n (%)	3 (10.3)	3 (9.4)	0	1 (7.7%)	2 (2.9)	2 (3.0)
Notable harms						
Hyperphosphatemia	0	0	0	0	4 (5.9)	0
Ectopic mineralization	0	0	1 (3.8)	0	0	0

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks	Placebo
Hypersensitivity	11 (37.9)	6 (18.8)	10 (38.5)	4 (30.8)	4 (5.9)	4 (6.1)
Injection-site reactions	15 (51.7)	0	10 (38.5)	19 (73.1)	8 (11.8)	8 (12.1)
Headache	10 (34.5)	6 (18.8)	18 (69.2)	1 (7.7)	9 (13.2)	5 (7.6)
Restless leg syndrome	0	0	0	0	8 (11.8)	5 (7.6)

6MWT = 6-minute walk test; BPI = Brief Pain Inventory; CI = confidence interval; LLN = lower limit of normal; LS = least squares; NA = not applicable; NR = not reported; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SAE = serious adverse event; SD = standard deviation; SF-10 = Short Form (10) Health Survey for Children; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Outcome not adjusted for multiplicity.

[b] The P value is from Cochran-Mantel-Haenszel testing for association between achieving mean serum phosphorus levels above the LLN and treatment group, adjusting for the actual randomization stratification of BPI average pain and region.

[c] This outcome was tested at a level of significance of 0.05, and it was not found statistically significant.

[d] This outcome was tested at a level of significance of 0.025, and it was not found statistically significant.

[e] This outcome was tested at a level of significance of 0.0167, and it was not found statistically significant.

Source: Clinical Study Reports for studies CL301, CL201, CL205, and CL303.[10-13]

Critical Appraisal

There were a number of limitations noted for these studies. First, studies CL301, CL201, and CL205 were open-label studies; therefore, patients were aware of their treatment allocations. As a result, the evaluation of patient-reported outcomes (such as the scales measuring pain, fatigue, or HRQoL) or AEs may have been affected by reporting bias, particularly for the within-group comparisons to baseline (studies CL201 and CL205). On the other hand, the fact that the assessments of RSS and RGI-C were conducted by radiologists who were blinded to patient identity, patient treatment status, and the timing of the radiographs would have limited investigator bias for these two outcomes.

Second, except for Study CL303, which included the change from baseline to week 24 in BPI worst pain, WOMAC stiffness, and WOMAC physical function scores in its adjustment for multiple testing, there was no control for multiplicity among the other secondary outcomes analyzed or among all secondary outcomes in studies CL301, CL201, and CL205. Therefore, results for these end points should be interpreted with consideration of the potential for inflated type I error.

Patients in the placebo arm of Study 303 did not receive any active or supportive treatment. However, in clinical practice, symptomatic patients might receive conventional therapy of oral phosphate supplements and active vitamin D analogues. Given that patients in the placebo treatment group did not receive oral phosphate supplements, and that patients had to have serum phosphorus levels less than the LLN (0.81 mmol/L) to be eligible to enrol, the CL303 study was biased in favour of the burosumab treatment group, especially for the primary outcome (the proportion of patients achieving mean serum phosphorus levels above the LLN). The findings of the study may not reflect the comparative effectiveness that would be achieved in the real-world setting.

Indirect Comparisons

No indirect comparisons were identified or submitted by the sponsor.

Other Relevant Evidence

Description of Studies

An ongoing, open-label, single-arm study (CL304, N = 14) assessed the effectiveness and safety of burosumab treatment on bone quality and osteomalacia associated with XLH in adult patients. To be eligible, patients' skeletal pain was required to be attributed to XLH and associated osteomalacia. Patients who had received oral phosphate and active vitamin D therapy within two years prior to enrolment were excluded. All eligible patients received burosumab 1 mg/kg every four weeks for 48 weeks. After completing the open-label treatment period, patients continued into an additional 48-week treatment extension period until week 96. Results up to week 48 are presented in this review. One patient discontinued the study before the week 48 visit.

The extension periods of studies CL201 and CL303 were designed to evaluate the long-term efficacy and safety of burosumab in children or adults with XLH. During these periods, patients who had completed the original randomized period were allowed to receive open-label burosumab therapy up to 216 weeks (Study CL201; results up to week 160 are presented) or 48 weeks (Study CL303; results up to week 48 are presented).

In the extension period of Study CL201, pediatric patients aged five years to 12 years who received burosumab every two weeks during the original randomization period continued to receive the same dose at the same interval. For patients originally assigned to received burosumab every four weeks, their regimen of burosumab in the extension period was initiated at week 64 using 60% of the most recent monthly dose every two weeks. (This group is referred to as the every-four-weeks-followed-by-every-two-weeks group). In Study CL201, all 52 patients entered the extension phase (26 patients in each treatment group) and completed burosumab therapy at the end of week 160.

In the extension period of Study CL303, 133 adult patients who enrolled in the randomized period entered the extension phase. Among them, 67 who received burosumab in the original randomization period continued burosumab treatment using the same dosing regimen, 1.0 mg/kg every four weeks (referred to as the continuing-on-burosumab group). Sixty-six patients who received placebo during the randomization period switched to burosumab 1.0 mg/kg every four weeks in the extension period (referred to as the placebo-followed-by-burosumab group). In total, 126 patients completed burosumab therapy at the end of week 48 in Study CL303 — 63 from each treatment group. Therefore, four patients from the continuing-on-burosumab group and three patients from the placebo-followed-by-burosumab group discontinued during the extension phase. Change from baseline refers to the baseline values in the placebo-controlled treatment period of the study.

Efficacy Results

Patient-Reported Outcome Measures

In Study CL304, there was a statistically significant improvement in the BPI worst pain scores from baseline to week 48 (LS mean change: −1.9; 95% CI, −3.17 to −0.55; P = 0.0013), indicating a reduced intensity of the worst pain from baseline; however, the change from baseline did not exceed the MCID for BPI worst pain scores of a 2-point change. In addition, the mean change in BPI pain severity and pain interference scores were statistically significantly reduced from baseline, indicating an improvement in severity of pain and the impact of pain on daily function in the study population. The LS mean change in BFI worst fatigue score from baseline was −1.6 (95% CI, −2.82 to −0.30; P = 0.0156),

indicating a reduced worst fatigue intensity from baseline. In addition, the LS mean change in BFI global fatigue score from baseline was −1.2 (95% CI, −2.33 to −0.08; P = 0.0359), indicating an improvement in fatigue in the study population. However, MCIDs for the BPI pain severity, BPI pain interference, BFI worst fatigue, or BFI global fatigue scores were not identified; therefore, the clinical importance of the improvement in these outcomes is unknown. The open-label study design and lack of comparator group add to the uncertainty in the interpretation of the study results.

In the extension period of Study CL201, the LS mean changes in Pediatric Orthopaedic Society of North America (POSNA)–Pediatric Outcomes Data Collection Instrument (PODCI) scores from baseline to week 160 were 13.18 (95% CI, 10.48 to 15.89; P < 0.0001) and 12.72 (95% CI, 9.69 to 15.75; P < 0.0001) for sports and physical functioning and pain and comfort scales, respectively, indicating improved functional ability and decreased pain. The mean change from baseline in the PHS of the SF-10 was 7.09 (standard error [SE] = 1.95), and the mean change from baseline in the PSS was 2.06 (SE = 1.22), suggesting an improvement in physical and psychosocial HRQoL from baseline in the study population. However, MCIDs for the POSNA-PODCI scores and the PHS and PSS of the SF-10 were not identified; therefore, the clinical importance of the improvement in these outcomes is unknown. In addition, the study results should be interpreted with caution, given the significant uncertainty due to the open-label study design and lack of comparator group.

In the Study CL303 extension period, the LS mean changes in BPI worst pain scores from baseline to week 48 were −1.1 (95% CI, −1.51 to −0.66; P < 0.0001) and −1.5 (95% CI, −1.98 to −1.09; P < 0.0001) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively, indicating a reduced intensity of worst pain from baseline in both groups. However, the improvement in BPI worst pain was not considered clinically important, given the MCID of a 2-point change for this outcome. In addition, the LS mean changes in BPI pain severity scores and BPI pain interference scores were statistically significantly reduced from baseline in the continuing-on-burosumab group and the placebo-followed-by-burosumab groups at week 48, indicating an improvement in severity of pain and the impact of pain on daily function in both groups.

Results of the BFI worst fatigue scores and BFI global fatigue scores indicated an improvement in fatigue in both groups (a statistically significant change was not detected in the continuing-on-burosumab group for the BFI global fatigue score). Results of the WOMAC physical function and stiffness scores also indicated an improvement in in both groups from baseline, where, at week 48, the LS mean changes in WOMAC physical function scores from baseline were −7.8 (95% CI, −11.97 to −3.55; P = 0.0003) and −6.4 (95% CI, −11.94 to −0.76; P = 0.0259) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively. The LS mean changes in WOMAC stiffness scores from baseline were −16.0 (95% CI, −22.53 to −9.53; P < 0.0001) and −15.3 (95% CI, −22.23 to −8.35; P < 0.0001) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively. Due to the lack of MCID for WOMAC, the clinical importance of these improvements is unknown. In addition, the study results should be interpreted with caution, given the significant uncertainty due to the open-label study design and lack of comparator group.

Serum Phosphorus Levels

In Study CL304, 13 patients (92.9%) achieved mean serum phosphorus levels above the LLN (0.81 mmol/L) at the midpoint of dose interval between baseline and week 24. At the

end of week 48, the LS mean change from baseline in serum phosphorus concentration was 0.06 mmol/L (SE 0.025), representing a percentage change of 11% from baseline in the study population.

In the Study CL201 extension period, the serum phosphorus level statistically significantly increased from baseline to week 160; the mean change was 0.33 mmol/L (standard deviation [SD] = 0.116 mmol/L]). In addition, 36 patients (69.2%) reached the normal range of 1.03 mmol/L to 1.97 mmol/L at week 160.

In the Study CL303 extension period, the LS mean changes from baseline in serum phosphorus concentration were 0.11 mmol/L (95% CI, 0.06 to 0.16) and 0.13 mmol/L (95% CI, 0.08 to 0.19) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively. The proportion of patients with mean serum phosphorus above the LLN across midpoints of dose intervals was 83.8% in the continuing-on-burosumab group and 89.4% in the placebo-followed-by-burosumab group.

Radiographic Changes

In the Study CL201 extension period, the LS mean changes from baseline to week 160 in the every-two-weeks group were −0.98 (95% CI, −1.23 to −0.73), −0.27 (95% CI, −0.40 to −0.14), and −0.70 (95% CI, −0.91 to −0.50) for the RSS total score, RSS wrist score, and RSS knee score, respectively; the LS mean changes in the every-four-weeks-followed-by-every-two-weeks group were −0.83 (95% CI, −1.07 to −0.60), −0.20 (95% CI, −0.29 to −0.10), and −0.62 (95% CI, −0.80 to −0.43) for the RSS total score, RSS wrist score, and RSS knee score, respectively, with $P < 0.0001$. Overall, the percentage of RSS responders, defined as those with a reduction in RSS total score from baseline of at least 1.0 point, was 57.1% in the every-two-weeks group and 60% in the every-four-weeks-followed-by-every-two-weeks group at week 160.

The RGI-C global score (mean of 1.92 [95% CI, 1.70 to 2.14; $P < 0.0001$] for patients taking burosumab every two weeks and mean of 1.86 [95% CI, 1.63 to 2.10; $P < 0.0001$] for those taking burosumab every four weeks followed by every two weeks), the RGI-C wrist score (mean of 1.78 [95% CI, 1.52 to 2.04; $P < 0.0001$] for patients taking burosumab every two weeks and mean of 1.83 [95% CI, 1.57 to 2.09 $P < 0.0001$] for those taking burosumab every four weeks followed by every two weeks), and the RGI-C knee score (mean of 2.01 [95% CI, 1.80 to 2.21; $P < 0.0001$] for patients taking burosumab every two weeks and mean of 1.85 [95% CI, 1.62 to 2.08; $P < 0.0001$] for those taking burosumab every four weeks followed by every two weeks) were all positive, indicating healing of rickets from baseline to week 160. However, an MCID for the RSS or RGI-C was not identified for patients with XLH; therefore, the clinical importance of the improvement in these outcomes is unknown.

Mobility Measurement

In the Study CL201 extension period, a statistically significant increase from baseline to week 160 in the distance walked within six minutes was observed for both groups: 57.4 m (95% CI, 38.1 to 76.6) in the every-two-weeks group and 56.1 m (95% CI, 32.6 to 79.6) in the every-four-weeks-followed-by-every-two-weeks group. The improvement was considered clinically meaningful, giving an MCID of 31 m in the pediatric population.

In the Study CL303 extension period, the LS mean change from baseline in the distance walked within six minutes was 31 m (95% CI, 16.9 to 44.1) and 20 m (95% CI, 3.0 to 37.4) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group,

respectively. The improvement was considered clinically relevant for the continuing-on-burosumab group, but not for the placebo-followed-by-burosumab group, based on an MCID of 31 m for the adult population.

Fractures/Pseudofractures

In Study CL304, there were four cases of active pseudofractures at baseline. At the end of 48 weeks of treatment with burosumab, three of them had healed, while data for the fourth patient were missing.

In the Study CL303 extension period, at week 48, 72.4% of the patients in the continuing-on-burosumab group with active pseudofractures at baseline had full healing compared to 52.9% of those in the placebo-followed-by-burosumab group. For patients with active fractures at baseline, 50% in both groups had full healing at week 48.

Change in Osteomalacia

In Study CL304, 11 patients had osteomalacia as determined by evaluation of the iliac crest bone biopsy at baseline. At week 48, the mean osteoid volume/bone volume (OV/BV) had statistically significantly decreased from baseline (mean change –14.9% [SD 10.97]). In addition, osteoid thickness (O.Th) had statistically significantly decreased from baseline (mean change –5.65 µm [SD 2.76]). Although an MCID for change in OV/BV in the study population was not identified, reductions in osteoid volume and thickness are essential for healing of osteomalacia, which is required for pseudofracture and fracture prevention and healing. Therefore, reduction in OV/BV can translate to important clinical benefits, such as relief in skeletal pain, prevention of pseudofracture or fracture, or improvement in HRQoL. However, it is uncertain to what extent this might happen.

Harms Results

In Study CL304, all patients reported at least one AE at the data cut-off date of August 30, 2017. The most commonly reported AEs included procedural pain (50%), arthralgia (36%), pain (36%), back pain (29%), and muscle spasms (29%). Two patients reported SAEs — one paresthesia and one migraine.

For the extension periods in studies CL201 and CL303, no patients withdrew from the study or from treatment due to AEs. No deaths were reported. The AEs of particular interest included ISRs, hypersensitivity, hyperphosphatemia, ectopic mineralization, and restless leg syndrome.

In the Study CL201 extension period, all 52 patients reported at least one AE. The most commonly reported AEs included headache (75%), cough (69%), vomiting (56%), arthralgia (54%), nasopharyngitis (54%), pain in extremity (52%), ISR (50%), oropharyngeal pain (50%), pyrexia (48%), upper respiratory tract infection (48%), injection-site erythema (44%), and rhinorrhea (42%). One patient (3.8%) in the every-four-weeks-followed-by-every-two-weeks group reported SAEs.

In the Study CL303 extension period, all patients in the continuing-on-burosumab group and 95.5% of patients in the placebo-followed-by-burosumab group reported at least one AE. The most commonly reported AEs included arthralgia (23.9%), nasopharyngitis (22.4%), headache (20.1%), back pain (16.4%), tooth abscess (13.4%), and fatigue (13.4%). There were seven patients (10.3%) in the continuing-on-burosumab group and eight patients (12.1%) in the placebo-followed-by-burosumab group who reported SAEs.

Critical Appraisal

The main limitations associated with Study CL304 and the extension periods of studies CL201 and CL303 arise from their open-label design, lack of comparator groups, and small sample size. The absence of a comparator group makes it challenging to interpret small changes from baseline, particularly in long-term studies involving children (Study CL201) where maturation may be responsible for changes in the relevant outcomes. One source of bias results from the subjectivity of outcome measures for the within-group comparisons to baseline in the studies, particularly for those self-reported questionnaires on pain, fatigue, and physical function, such as the BPI, BFI, or WOMAC.

Patients enrolled in the studies appear to be similar, in general, to patients with XLH in Canada.

There was lack of information about the use of burosumab in the adolescent population, as no clinical trials in the burosumab development program enrolled patients aged 13 years to 17 years.

Conclusions

Studies CL301 and CL303 provided evidence of the efficacy and safety of burosumab in pediatric and adult patients with XLH, respectively. Pediatric patients who received burosumab every two weeks showed improvements in radiographic end points (as measured by the RSS and the RGI-C Scale scores, improved serum phosphorus concentration, and reduced lower extremity deformities); however, there was uncertainty in improved growth and improved mobility compared with oral phosphate and active vitamin D treatment. In addition, burosumab did not show meaningful improvement in HRQoL or other important patient-reported outcomes. Long-term extension studies support the sustainability of these treatment effects.

In adult patients, there were significant improvements in serum phosphorus concentrations and patient-reported stiffness compared to placebo at week 24. There were likely clinically significant improvements in patients with burosumab in terms of healing of active and non-active fractures and pseudofractures compared to placebo. However, when compared with placebo, burosumab did not show improvement in pain or fatigue. In both the pediatric and adult patients, no withdrawal from treatment or from the studies for AEs was reported during the studies or their extension phases. There were also no safety signals among AEs of special interest (including hyperphosphatemia, ectopic mineralization, hypersensitivity, and ISRs). There were no deaths. Safety data from the studies did not demonstrate any notable concerns about SAEs. Conclusions regarding the long-term efficacy and safety of burosumab in patients with XLH are limited due to the short duration of treatment. Ideally, several more years of treatment with follow-up would highlight whether burosumab offers long-term improvements and a better safety profile compared to the current conventional therapy.

Introduction

Disease Background

XLH is a rare, chronically debilitating genetic disorder. It is characterized by renal phosphate wasting and consequent defective bone mineralization caused by inactivating mutations in PHEX.[1-4] In the absence of functional PHEX, patients with XLH produce excess FGF23, leading to impaired conservation of phosphate and consequent hypophosphatemia.[2-4,14] Excess FGF23 also suppresses $1,25(OH)_2D$ production, resulting in decreased intestinal absorption of calcium and phosphate.[1-4]

Patients usually develop clinical symptoms during the first or second year of life.[3] XLH in children is characterized by vitamin D–resistant rickets, and results in variable degrees of delayed walking, waddling gait, leg bowing, enlarged cartilages, bone pain, craniosynostosis, dental abscesses, and impaired growth.[1,3,15] Adults with XLH can have symptoms such as bone and/or joint pain, fractures, mineralization defects (such as osteomalacia), enthesopathy, severe dental anomalies, hearing loss, and fatigue.[1,3,4] Adults with XLH are susceptible to pseudofractures and fractures due to a combination of osteomalacia and skeletal deformities ensuing from rickets in childhood.[16]. These musculoskeletal abnormalities in adults with XLH result in pain and stiffness, impaired mobility and physical function, and reduced HRQoL.[17,18]

As is the case with many rare diseases, 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.[5] The estimated prevalence of hypophosphatemic rickets in southern Denmark is 4.8 per 100,000 persons (children and adults).[6] There are no known reported prevalence estimates for Canada.

Standards of Therapy

Prior to the approval of burosumab in Canada, there were no approved treatments for XLH that targeted the underlying pathophysiology of excess FGF23. Supportive care pharmacotherapy has been provided, with the aim of counteracting the consequences of excess FGF23. Multiple daily doses of oral phosphorus supplements are necessary to compensate for renal phosphate wasting. Active vitamin D analogues (alfacalcidol or calcitriol) are also required to counter $1,25(OH)_2D$ deficiency.[1,3] Treatment with calcimimetics might be considered in patients with persistent secondary or tertiary hyperparathyroidism.[3]

These conventional therapies are considered inadequate in the treatment of XLH because they do not correct the underlying pathophysiology of excess FGF23.[1,15] Supplementation transiently increases serum phosphorus levels, but is associated with gastrointestinal side effects and risks of metabolic and endocrine abnormalities, such as hypercalciuria, nephrocalcinosis, and hyperparathyroidism.[1,3] In children, phosphorus administration is required three to five times in a 24-hour period; the optimal dose has not been determined, and phosphorus can lead to gastrointestinal side effects.[1,3] Active vitamin D supplementation is associated with an increased risk of hypercalciuria and nephrocalcinosis.[3] In addition to the complications noted earlier, consistent treatment with both oral phosphate and vitamin D analogues may not normalize bone growth.[1] Furthermore, vitamin D administration, as well as phosphate, may further increase FGF23.[19]

Drug

Burosumab is a recombinant human immunoglobulin G subclass 1 monoclonal antibody that binds to the N-terminal domain of FGF23. This inhibits the biological activity of FGF23, thereby increasing both renal phosphate reabsorption and the serum concentration of $1,25(OH)_2D$.[20]

Burosumab is indicated for the treatment of XLH in adult and pediatric patients one year of age and older.[7]

The Health Canada–recommended starting dose of burosumab in pediatric patients with XLH (from one year to less than 18 years of age) is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg; the maximum dose is 90 mg. After initiation of treatment with burosumab, fasting serum phosphorus need to be measured every four weeks for the first three months of treatment, and thereafter as appropriate. If serum phosphorus is within the lower limit of the reference range for age, treatment continues with the same dose. Patient weight should be checked periodically to ensure that the proper total dose for patient weight is being administered. If serum phosphorus is below the 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. The calculated dose should be rounded to the nearest 10 mg, with a maximum dose of 90 mg. Fasting serum phosphorus levels should be reassessed four weeks after dose adjustment. The burosumab dose should not be adjusted more frequently than every four weeks. If serum phosphorus is above the reference range for age, the next dose should be withheld, and the serum phosphorus level should be reassessed in four weeks. The patient must have a serum phosphorus level below the reference range for age to reinitiate burosumab. Once the serum phosphorus level is below the reference range for age, treatment may be restarted at half the dose level previously administered. The serum phosphorus level needs to be reassessed four weeks after dose adjustment. If the level is below the reference range for age after the re-initiation dose, the dose can be increased gradually according to the dose increase instructions.[7]

The Health Canada–recommended starting dose of burosumab in adult patients with XLH (18 years of age and older) is 1 mg/kg of body weight rounded to the nearest 10 mg, administered every four weeks; the maximum dose is 90 mg. Dose recalculation should be performed if the patient's weight changes by plus or minus 10%. After initiation of treatment with burosumab, starting two weeks post-dose, fasting serum phosphorus levels should be measured monthly for the first three months of treatment, and thereafter as appropriate. If serum phosphorus levels are within the normal range, the same dose should be continued. Burosumab should not be administered at doses greater than 1 mg/kg in adults. If serum phosphorus levels are above the normal range, the next dose should be withheld, and the serum phosphorus level should be reassessed after four weeks. The patient must have a serum phosphorus level below the normal range to reinitiate burosumab. Once the serum phosphorus level is below the normal range, treatment may be restarted at half the previous starting dose up, to a maximum dose of 40 mg every four weeks. Serum phosphorus should be reassessed two weeks after any change in dose. The burosumab dose should not be adjusted more frequently than every four weeks. [7]

Burosumab is administered by SC injection and should be administered by a health professional.[7]

Table 2: Key Characteristics of Burosumab, Alfacalcidol, Calcitriol, Sodium Phosphate, and Cinacalcet Hydrochloride

	Burosumab (Crysvita)	Alfacalcidol (ONE-ALPHA)	Calcitriol (Calcitriol–Odan)	Sodium phosphates (Phoslax)	Phosphate effervescent[a]	Cinacalcet hydrochloride (Sensipar)
Mechanism of action	An antibody that binds to and inhibits the biological activity of FGF23	A synthetic analogue of 1,25-dihydroxyvitamin D, the active form of vitamin D. It stimulates intestinal calcium and phosphorus absorption, resorbs bone at high doses, and possibly enhances renal calcium reabsorption.	Calcitriol is synthesized 1,25-dihydroxyvitamin D. It stimulates intestinal calcium and phosphorus absorption, resorbs bone at high doses, and possibly enhances renal calcium reabsorption.	Natural product of sodium and phosphate	Natural product of sodium and phosphate	A synthetic molecule that directly lowers PTH levels by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium
Indication	For the treatment of XLH in adult and pediatric patients 1 year of age and older[b]	For management of hypocalcemia, secondary HPT[b]	For management of hypocalcemia, secondary HPT, and forms of familial hypophosphatemia[b]	Correction of hypophosphatemia[c]	Correction of hypophosphatemia[c]	Indicated for the treatment of secondary or tertiary HPT[c]
Route of administration	SC	Capsules, oral drops, or injection	Oral	Oral	Oral	Oral
Recommended dose	0.8 mg/kg of body weight rounded to the nearest 10 mg, administered by SC injection every 2 weeks in pediatric patients (1 year to less than 18 years of age). The minimum starting dose is 10 mg up to a maximum dose of 90 mg.	In children, 40 ng/kg/day to 60 ng/kg/day divided once or twice a day[c] In adults, 0.75 mcg to 1.5 mcg daily[3]	In children, 20 ng/kg/day to 30 ng/kg/day divided in 2 doses[c1] In adults, 0.50 to 0.75 µg daily[3]	In children, 20 mg/kg/day to 40 mg/kg/day (in 3 to 5 divided doses) [c1] In adults, 750 mg to 1,600 mg daily[c3]	In children, 20 mg/kg/day to 40 mg/kg/day (in 3 to 5 divided doses) [c1] In adults, 750 mg to 1,600 mg daily[c3]	Starting oral dose is 30 mg once daily, titrated every 2 weeks to 4 weeks to a maximum dose of 180 mg once daily

	Burosumab (Crysvita)	Alfacalcidol (ONE-ALPHA)	Calcitriol (Calcitriol–Odan)	Sodium phosphates (Phoslax)	Phosphate effervescent[a]	Cinacalcet hydrochloride (Sensipar)
	1 mg/kg of body weight rounded to the nearest 10 mg to a maximum dose of 90 mg, administered by SC injection every 4 weeks in adult patients (18 years of age and older). Should not be administered at doses greater than 1 mg/kg in adults or more than 90 mg. In both pediatric and adults, the dose of burosumab may be adjusted based on serum phosphorus levels, with a maximum dose of 90 mg.					
Serious adverse effects or safety issues	Hyperphosphatemia, hypersensitivity, injection-site reactions	Hypercalcemia	Hypercalcemia, hypersensitivity reactions	Can cause diarrhea at high doses[c]	Can cause diarrhea at high doses[c]	Hypocalcemia, hypotension, and/or worsening heart failure

FGF23 = fibroblast growth factor 23; HPT = hyperparathyroidism; PTH = parathyroid hormone; SC = subcutaneous; XLH = X-linked hypophosphatemia.

[a] Brand name: JAMP Phosphate Effervescent tablets.

[b] Health Canada–approved indication.

[c] As per the clinical expert.

Source: Product monographs,[7,22-24] natural health product ,[25-27] Carpenter et al.,[1] Haffner et al.[3]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

With support from the XLH Network, one patient group, CORD, provided patient input for this submission. CORD is a national network for organizations representing all Canadians with rare disorders (https://www.raredisorders.ca/). It works with governments, researchers, clinicians, and industry to promote research, diagnosis, treatment, and services for those with rare disorders in Canada. The XLH Network is a worldwide support organization for people living and dealing with XLH. Its mission is to promote XLH awareness and education for affected families, medical professionals, and the community; to support physicians and other health care providers for better diagnosis and treatment; to create resources and a community for affected individuals and their families so they can understand and cope with the complications of the disease; and to foster the search for a cure. The organization reported that it had no help from outside its organization to collect and analyze data or complete the submission. Over the past two years, it did not receive funding from pharmaceutical companies or organizations.

2. Condition-Related Information

Because there is no established XLH Network in Canada, CORD identified patients with XLH and their families by connecting with the international XLH Network, a registered charity in the US. Three methods were used to recruit participants: direct requests to Canadian patients and families, who then recruited other families; posts on the Facebook page of the XLH Network; and direct outreach by clinicians treating XLH patients in Canada, including those who had taken part in clinical trials for burosumab (Crysvita). Information was collected primarily through an online survey as well as individual interviews with patients and parents who had experience with Crysvita. Overall, 70 people responded to the online survey, 20 of whom lived in Canada. Among the 70 respondents, 67% had been diagnosed with XLH, while 4% said they were not (yet) diagnosed with XLH, but had symptoms consistent with it. About 27% of survey respondents were caregivers for patients with XLH. One person was unsure as to her diagnosis and another indicated hers was a spontaneous case.

Most of the respondents had been diagnosed a long time ago: 87% had been diagnosed under the age of 12 years old; about 4% were diagnosed between the ages of 12 years and 18 years; and 9% were over 30 years of age at diagnosis. In terms of time since diagnosis, 80% had been diagnosed more than 30 years ago; 11% had been diagnosed 18 years to 30 years ago; 2% had been diagnosed between three years and 18 years ago; and 4% had been diagnosed less than three years ago. While the expected gender ratio of XLH is 2:1 females to males, the respondents to this survey were overwhelming female (88%). Because XLH is a genetic disorder, many of the respondents talked about generations of XLH in the family as well as impacts on other relatives. However, many cases reported in this submission were spontaneous (mutations), with no family history.

According to the respondents, the most common symptoms of XLH include chronic debilitating pain, bone and joint deformities in legs and spine, severe dental problems, fractures and stiffness, short stature, hearing problems, and osteoarthritis with aging. Treatments (surgeries and medication regimes) for XLH were associated with significant

social, educational, or work challenges, financial difficulties, and psychological impacts on patients and their families. One major challenge reported by respondents was the time required to manage the disease (diagnosis, testing, treatment, and time to travel to specialty sites). This translates to time taken from work for patients and family members, which also leads to financial impacts. In addition, children need to be dosed while at school and during the night. Furthermore, XLH is a costly disease in terms of over-the-counter medications that may be needed but not covered by insurance. For older adults, the physical symptoms (bone and joint damage) accumulate, as do the psychological impacts. All of these have serious, deleterious impacts on quality of life for patients and their families.

Respondents were asked to rate the degree to which they experienced difficulties or problems associated with XLH on a 5-point scale ("no problem, never," "minor, infrequent," "moderate, sometimes," "serious, frequent," or "incapacitating, regularly"), where higher scores indicated more difficulties. The average rating of difficulty was 4.2 out of 5.

Some quotes from the patient group:
"She was medicated 5x throughout the day and night. This was difficult as we had to wake her after midnight to medicate her and then again early in the morning. She required medication at school each day and the school was not consistent in administering it. We ended up removing her from the school to ensure she receives her medication."

"XLH has significantly limit[ed] my mobility. I have to walk with additive devices at all times, have had several falls and broken bones along with severe pain. I need help daily from my family and need help with my personal hygiene care. XLH impacts myself and my family every minute of every day."

"Due to severe malformation of my back/spine and knee, I live with constant pain and yes, shame. It has worsened considerably when entering my seventies."

3. Current Therapy-Related Information

Prior to Crysvita, there were no specific therapies for the treatment of XLH. The vast majority of survey respondents reported having received, currently or in the past, phosphate supplements (92%) and calcitriol supplements (88%) to augment phosphate and calcium. Most had received or were currently receiving vitamin D supplements. Fewer had received growth hormone therapy (12%). Respondents were asked to rate the effectiveness of each therapy in managing their XLH symptoms on a 5-point scale from "not at all" to "very well." Ten percent felt phosphate supplements and calcitriol supplements worked "well" or "very well," while 30% to 40% felt the supplements were somewhat effective and 40% felt they had poor impact. The feedback on vitamin D was about the same, with a slightly larger percentage of respondents rating the benefits as "not at all." In terms of corrective therapy, almost all respondents (98%) reported undergoing dental procedures (often very serious and invasive). Most (60%) had undergone corrective surgery on their legs, including some spinal surgery, while 10% reported surgery to address skull deformities. One-third of respondents (33%) said dental procedures had performed "well" or "very well" in addressing their presenting symptoms or problems. Among those who had received corrective surgery on their legs, about one-quarter (27%) felt the intervention had worked "well" or "very well" to address the problem. Overall, existing therapies (prior to Crysvita) had only, at best, moderate benefit in terms of addressing symptoms or reducing disease progression, with many respondents feeling the impacts were limited or very limited. This was expressed by patients of all ages (and by caregivers of patients of all ages), although the impact of the

disease was progressive, and older adults were considerably less mobile, less engaged, and more depressed.

More than two-thirds of respondents knew Crysvita well or very well, while less than 5% said they had not heard of the new therapy. The patient group indicated that Canadian patients were as aware of Crysvita as their American and other international counterparts, with only 10% having little or no awareness. However, access to the therapy is considerably different. For the respondents as a whole, about one-third (23 patients) had received or were currently receiving Crysvita. Among these, 20 were from the US or other countries; only three were from Canada. The Canadian patients had accessed Crysvita through clinical trials. Respondents who had experience with Crysvita were overwhelmingly positive about the impact on pain, fractures, dental problems, and mobility. Even adult patients with existing damage reported improvements in capacity and little or no new damage. Most of the patients receiving Crysvita reported experiencing no side effects, and none reported having side effects that were serious or unresolvable. A few reported injection-site rashes or irritations during first-time use; a couple of others experienced occasional nausea. Three patients reported restless leg syndrome (which was bothersome, but described as *"a fine trade-off from pain relief").*

"My body has already been ravaged with the effects of XLH. While on Crysvita my pain levels were less, my fatigue was greatly reduced, and life in general was a bit improved which had a very positive impact on my emotional health as well. Since being off Crysvita for 5 months now, I have increased bone pain particularly in the long bones of my arms and legs. I'm fatigued and fall asleep most evenings when watching programs on television."

4. Expectations About the Drug Being Reviewed

Most respondents expected that Crysvita would reduce or eliminate their symptoms, including pain, bowed legs, fractures, and fatigue. Most importantly, they expected that it would stop disease progression by addressing the underlying cause. Respondents felt it was "very important" or "important" for all appropriate XLH patients to have access to Crysvita. The therapy was characterized as "life-changing" by several respondents. About 90% said they would be willing to enrol in a follow-up program if on therapy.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). In addition, as part of the burosumab review, a panel of five clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place of the drug in therapy of (e.g., potential reimbursement conditions). A summary of this panel discussion is presented in the next section.

Description of the Current Treatment Paradigm for the Disease

Prior to the approval of burosumab in Canada, no approved treatments for XLH have targeted the underlying pathophysiology of excess FGF23. XLH is caused by mutations in the PHEX gene. The PHEX mutation causes an increase in the hormone FGF23, which inhibits phosphate transport in the kidney, causing phosphaturia and hypophosphatemia. The hypophosphatemia can lead to rickets and osteomalacia in children and adolescents, and to osteomalacia in adults. In addition, FGF23 inhibits renal $1,25(OH)_2D$ production, which may lead to decreased calcium and phosphate absorption in the gut, further contributing to rickets and osteomalacia. Consequently, the current treatment of XLH in pediatric and adult patients includes the use of oral phosphate supplements and active vitamin D analogues (calcitriol or alfacalcidol). It also emphasizes adequate nutritional intake of calcium to prevent or reverse rickets and osteomalacia. Oral phosphate supplements should always be provided with active vitamin D, as phosphate alone promotes secondary or even tertiary hyperparathyroidism. Occasionally in adults, supplemental oral calcium or a calcimimetic is needed, especially if parathyroid hormone (PTH) levels begin to increase during treatment. Therefore, conventional therapy does not directly modify the underlying disease mechanism; rather, it attempts to improve the low circulating serum phosphorus and calcitriol concentrations. In children, it is recommended that phosphate supplements be taken as frequently as possible, usually not less than five times per day, with one dose during the night. In adults, oral phosphate is usually given from two to a maximum of four times per day.

Treatment Goals

The ideal treatment in pediatrics should aim to prevent lower limb deformities with abnormal gait (to prevent surgery to correct deformity and to reduce pain and improve mobility), to improve the mineralization of bones (to prevent fractures later in life and reduce limb deformity), to reduce radiographic rachitic changes, to improve growth velocity, to reduce abnormal skull shape (dolichocephaly) due to rickets and osteomalacia, and to reduce dental abscesses due to odontomalacia.

The ideal treatment in adults should address osteomalacia, which causes bone pain and pseudofractures; osteoarthritis, which causes pain and stiffness; enthesopathy; and poor dental health, including abscesses and periodontitis. Therefore, the ideal treatment would improve HRQoL, increase ability to maintain employment and independence, and reduce the burden on caregivers.

Pediatric and adult patients treated with the conventional therapy of oral phosphate supplements and active vitamin D analogues often develop secondary hyperparathyroidism, which is associated with phosphate treatment (as a result of the induction of hypocalcemia). The parathyroid hyperplasia resulting from chronic secondary hyperparathyroidism can evolve into tertiary hyperparathyroidism, with hypercalcemia requiring parathyroid surgery or medical management. High-dose phosphate supplementation is also associated with poorly tolerated gastrointestinal side effects, including diarrhea. Patients treated with calcitriol might also develop hypercalciuria, nephrocalcinosis, nephrolithiasis, and, potentially, renal failure.

Unmet Needs

The conventional therapy of oral phosphate supplements and active vitamin D analogues can stimulate additional FGF23 secretion, resulting in a vicious cycle of increasing phosphate (and calcitriol) needs but an inability to normalize the serum phosphate or $1,25(OH)_2D$ completely. For pediatric patients, growth, limb deformities, joint pain and quality of life may improve with conventional therapy, but the treatment seldom normalizes phosphate levels or the mineralization of bones; nor does it prevent the long-term skeletal complications of XLH, such as dental disease, arthritic complications, and enthesopathy or spinous ligament calcification. In adult patients, osteoarthritis and enthesopathies are not generally addressed by current conventional therapy.

Furthermore, the frequency of the required administration of phosphate and calcitriol often results in poor compliance across all ages because phosphate treatment needs to be administered anywhere from twice per day to up to six times per 24-hour period, and calcitriol needs to be administered once or twice per day. In addition, the dose and frequency vary with the developmental stage of the patient and the individual response to therapy, as well as with the occurrence of AEs of the current treatment, as previously noted in the Treatment Goals section. As a result, treatments that are more convenient (i.e., less onerous than five times per 24-hour period), better tolerated, and reduce the risk of long-term skeletal and renal complications would be optimal.

Place in Therapy

Burosumab is an FGF23-blocking antibody that enhances renal phosphate transport, reducing urinary phosphate loss and increasing serum levels of phosphate. Additionally, burosumab increases $1,25(OH)_2D$ concentrations by preventing FGF23's inhibition of $1,25(OH)_2D$ production in the kidneys. Therefore, burosumab therapy would eliminate the need for phosphate and calcitriol therapy. Consequently, it would represent a therapy of choice rather than a therapy complementing the current therapy. It is anticipated that, consequently, burosumab would replace conventional therapies and significantly shift the current treatment paradigm.

The clinical experts thought that for patients younger than one year of age, patients with mild disease, pregnant or breastfeeding women, or patients with severe renal impairment or end-stage renal disease, it would be appropriate to try the conventional therapy of oral phosphate supplements and active vitamin D analogues first, then switch to burosumab if complications arose. For patients with severe disease, the clinical experts expected that burosumab would be used as the first-line treatment, given that it is an expensive medication that is relatively new and for which long-term safety data are lacking. In addition, only a small number of studies were available, and all clinical trials enrolled only a small number of patients. All clinical experts indicated that if more evidence became available, and if the cost of burosumab was not an issue, they would prescribe it for all patients as the first-line treatment regardless of severity, except for infants and pregnant or breastfeeding women.

Patient Population

The diagnosis of XLH requires clinical assessment, a family history, and a biochemical evaluation, including determination of levels of serum phosphate, calcium, alkaline phosphatase, parathyroid hormone, $1,25(OH)_2D$, creatinine, and FGF23. It also requires an index of urine phosphate reabsorption, such as the ratio of renal tubular maximum

reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR). If there is no documented history of XLH in the patient`s family, genetic testing to identify a PHEX mutation would confirm the clinical and biochemical diagnosis of XLH and avoid misdiagnosis. Children with rickets or hypophosphatemia are typically referred to pediatric specialists, including geneticists, endocrinologists, nephrologists, and orthopedic surgeons. In most cases, these physicians work in or are affiliated with a tertiary care centre. These physicians work collaboratively to ensure the correct diagnosis and treatment of XLH.

The pediatric and adult patients best suited for treatment with burosumab are symptomatic patients with reduced serum phosphate and $1,25(OH)_2D$ levels, confirmed PHEX mutation in the patient or in a directly related family member with appropriate X-linked inheritance, and elevated FGF23 levels. In addition, the panel indicated that pediatric patients should have an RSS total score of at least 2. Nevertheless, it may be difficult to determine a set of distinct characteristics for pediatric patients who would best respond to treatment with burosumab, given the limited data available. In addition, pediatric patients who have mild disease (defined as RSS total score less than 2) should not receive burosumab treatment. These patients would, nevertheless, need to be monitored and should be started on conventional therapy if required; if they had a decline in growth velocity, or any progression of deformity after receiving conventional therapy, they should be switched to burosumab, as long as there were no contraindications (e.g., severe renal disease).

The approach to the treatment of adult patients was variable among panel members. In one approach, burosumab treatment would be initiated only in those with severe manifestations (i.e., who have nephrocalcinosis, poor mobility, significant bone and joint pain, hyperparathyroidism, or radiographic evidence of osteomalacia with fractures or pseudofractures). In another approach, all adult patients with documented XLH would receive burosumab initially, regardless of severity. However, it was agreed that patients who have the most severe manifestations would likely respond best to treatment with burosumab.

It was felt that patients who are less than one year of age, who are asymptomatic, who have renal failure, and who are pregnant or breastfeeding should not receive burosumab.

Assessing Response to Treatment

For pediatric patients, in practice, clinicians would assess serum phosphate and $1,25(OH)_2D$ levels, an index of renal phosphate reabsorption, RSS, growth, limb deformities, fatigue, and mobility. A pediatric patient is considered a responder if the phosphate levels are normalized (lower reference interval), $1,25(OH)_2D$ levels are improved, and there is improved linear growth and healing of rickets. Radiographic X-rays would be conducted one year after the initiation of burosumab treatment; biochemical evaluation would be conducted every four to six months. The panel indicated that treatment response should be assessed yearly for renewal purposes.

For adult patients, in practice, clinicians would assess serum phosphate and $1,25(OH)_2D$ levels, an index of renal phosphate reabsorption, pain, physical function and stiffness, fractures or pseudofractures, and osteomalacia. Meaningful responses to treatment include decreased bone pain, increased mobility, radiologically documented prevention and healing of fractures and pseudofractures, and prevention of dental abscesses. Biochemical evaluation would be conducted every four to six months; once patients were stable on burosumab, then biochemical evaluation could be conducted once a year. Radiographic

assessment would also be conducted once a year. The panel indicated that the treatment response should be assessed yearly for renewal purposes.

Discontinuing Treatment

There are no long-term data to indicate how long burosumab will retain efficacy or whether it will cause adverse effects in the long term. Treatment discontinuation should be considered in cases of lack of response (e.g., due to development of neutralizing antibodies) or where unacceptable side effects are present (such as severe cutaneous reactions).

Prescribing Conditions

Burosumab for the treatment of XLH should be prescribed by specialists in endocrinology, genetics, rheumatology, or nephrology who have expertise in metabolic bone disease. The diagnosis of XLH and initial treatment with burosumab should take place in specialized clinics in tertiary care centres. However, the panel considered that patients could potentially receive burosumab injections at home once the initial responses have been monitored.

Clinical Evidence

The clinical evidence included in the review of burosumab is presented in three sections. Section 1, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes sponsor-submitted long-term extension studies and additional relevant studies/evidence that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of burosumab for the treatment of XLH in adult and pediatric patients one year of age and older.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adult and pediatric patients (1 year of age and older) with XLH
	
	Subgroups:
	• Adult patients with prior fracture versus those without prior fracture
	• Severity (e.g., based on rickets severity for pediatric patients, functional impairment, or pain)
	• Age
	  ○ Adults (≥ 18 years) versus pediatrics (< 18 years)
	  ○ Pediatrics (by age groups)

Intervention	Burosumab 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered by subcutaneous injection every two weeks in pediatric patients (1 year to less than 18 years of age). The minimum starting dose is 10 mg, up to a maximum dose of 90 mg. Burosumab 1 mg/kg of body weight, rounded to the nearest 10 mg, up to a maximum dose of 90 mg, administered by subcutaneous injection every four weeks in adult patients (18 years of age and older). Doses should not be greater than 1 mg/kg in adults, or more than 90 mg. In both pediatric and adult patients, the dose of burosumab may be adjusted based on serum phosphorus levels, with a maximum dose of 90 mg.
Comparators	For pediatric patients (1 year to less than 18 years of age): • Oral phosphate and active vitamin D analogues (calcitriol or alfacalcidol) • Placebo

Comparators	For adults: • Oral phosphate and active vitamin D analogues (calcitriol or alfacalcidol) ± calcimimetic placebo
Outcomes	**Efficacy outcomes for adults and pediatric patients:** • HRQoL based on a validated scale (for patients and caregivers)[a] • Pain (including bone pain, joint pain and stiffness, and dental pain)[a] • Fractures and pseudofractures[a] • Mobility • Neurological complications (including problems with hearing and balance) • Tooth loss and dental abscesses • Renal function • Phosphate homeostasis (e.g., serum phosphorus, serum $1,25(OH)_2D$) • Bone metabolism (e.g., BALP) • PTH levels • Osteoid volume and osteoid thickness • Fatigue[a] **Efficacy outcomes for pediatric patients only:** • Radiographic response (severity of rickets, radiographic appearance of rickets, and bowing)[a] • Growth (including height) **Harms outcomes:** AEs, SAEs, WDAEs, mortality, and notable harms or harms of special interest (hyperphosphatemia, ectopic mineralization, hypersensitivity, injection-site reactions, headache, and restless leg syndrome)
Study design	Published and unpublished phase III and IV RCTs

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; AE = adverse event; BALP = bone-specific alkaline phosphatase; HRQoL = quality of life; PTH = parathyroid hormone; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event; XLH = X-linked hypophosphatemia.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[28]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Crysvita (burosumab). Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform search portal.

No filters were applied to limit retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on August 14, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on December 11, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[29] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews,

Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH Common Drug Review clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4, Table 5, and Table 6. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

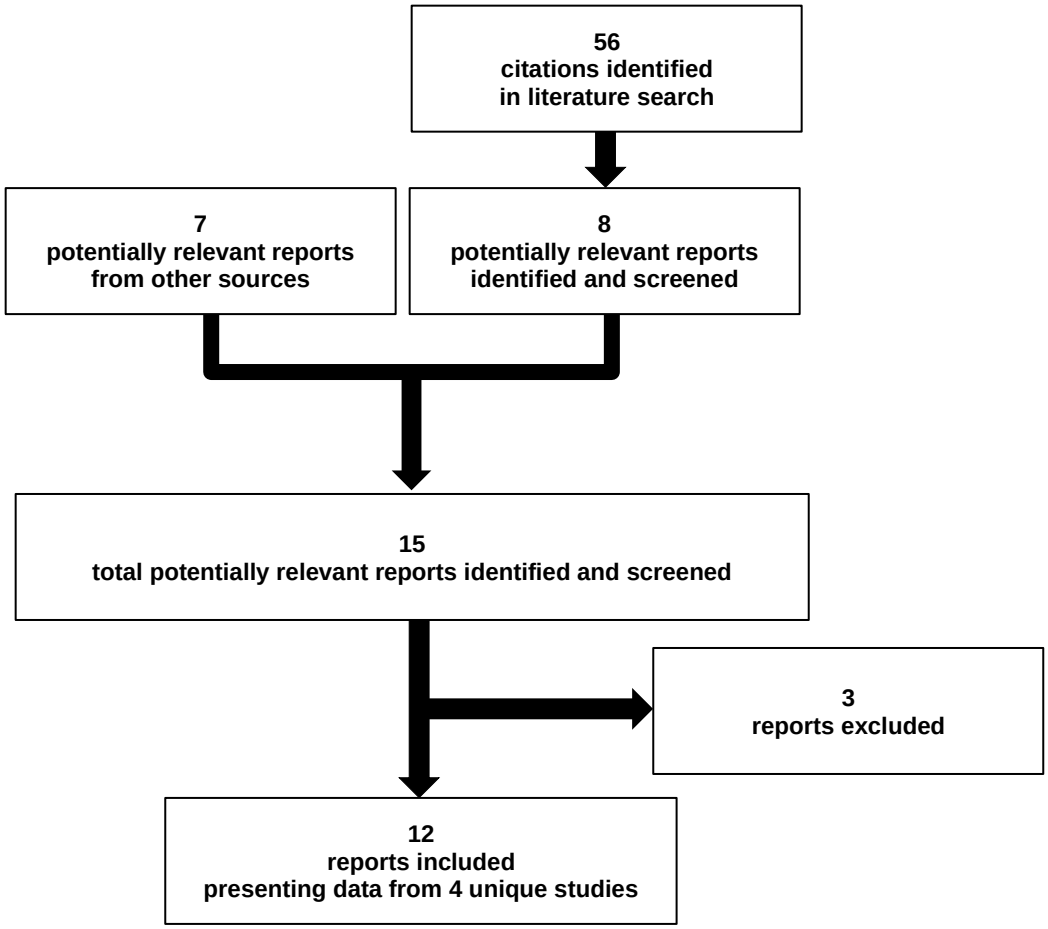


Table 4: Details of Study CL301

		Study CL301
Designs and populations	**Study design**	Phase III, open-label RCT
	Locations	Australia, Canada, Europe, and the US
	Randomized (N)	61
	Inclusion criteria	• Male or female, aged 1 year to ≤ 12 years, with radiographic evidence of rickets with an RSS total score of ≥ 2.0 • PHEX mutation or variant of uncertain significance in either the patient or a directly related family member with appropriate X-linked inheritance • Fasting serum phosphorus ≤ 3.0 mg/dL • Fasting serum creatinine below the age-adjusted ULN • Serum $1,25(OH)_2D$ above the (≥ 16 ng/mL) at the screening visit • Have received both oral phosphate and active vitamin D therapy for ≥ 12 consecutive months (for children ≥ 3 years of age) or ≥ 6 consecutive months (for children < 3 years of age) 7 days prior to the randomization visit
	Exclusion criteria	• Tanner stage 4 or higher in genitals, breast, or pubic hair, based on physical examination • Height percentile > 50th based on country-specific norms • Use of aluminum hydroxide antacids, systemic corticosteroids, acetazolamide, or thiazides within 7 days prior to the screening visit • Current or prior use of leuprorelin, triptorelin, goserelin, or other drugs known to delay puberty • Use of growth hormone therapy within 12 months before the screening visit • Presence of grade 4 nephrocalcinosis on renal ultrasound (grade 4 defined as stone formation: solitary focus of echoes at the tip of the pyramid) • Planned orthopedic surgery, including osteotomy, implantation, or removal of staples, 8-plates, or any other hardware, within the first 40 weeks of the study • Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits • Evidence of hyperparathyroidism • Use of medication to suppress PTH (e.g., cinacalcet, calcimimetics) within 2 months prior to the screening visit
Drugs	**Intervention**	The starting dose of burosumab SC injection was 0.8 mg/kg every two weeks, which could be increased to 1.2 mg/kg.
	Comparator(s)	Phosphate and active vitamin D administered orally several times daily
Duration	**Phase**	
	Open-label	64 weeks
	Follow-up	NA
	Extension	76 weeks
Outcomes	**Primary end point**	Change in rickets at week 40 as assessed by the RGI-C global score
	Secondary and exploratory end points	**Secondary:** • Proportion of patients with a mean RGI-C global score ≥ +2.0 (substantial healing) at week 40 and week 64 • Change in rickets at week 64 as assessed by the RGI-C global score • Change from baseline in RSS total score at week 40 and week 64 • Change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as assessed by the RGI-C long leg score at week 40 and week 64 • Change in standing height (or recumbent length in children < 2 years) from baseline to week 24, week 40, and week 64, in cm • Change in height-for-age z scores from baseline to week 24, week 40, and week 64

		Study CL301
		• Change in growth velocity from pre-treatment and post-treatment at week 40 and week 64 in cm/year • Serum phosphorus • Serum $1,25(OH)_2D$ • TmP/GFR • TRP • ALP • Change from baseline in the PROMIS pain interference, physical function mobility and fatigue domain scores (for patients ≥ 5 years of age at the screening visit) at week 24, week 40, and week 64 • Change from baseline in FPS-R (for patients ≥ 5 years of age at the screening visit) at week 24, week 40, and week 64 • Change from baseline in 6MWT total distance and percentage of predicted normal (for patients ≥ 5 years of age at the screening visit) at week 24, week 40, and week 64 **Exploratory:** • Change from baseline to post-baseline visits in the SF-10 physical summary score and psychosocial summary score for patients ≥ 5 years of age at the screening visit • Dental evaluation: number of dental events in dental caries, tooth extraction, root canal, dental abscesses, and gingivitis, assessed at baseline and post-baseline visits
NOTES	**Publications**	Imel et al.[30]

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; 6MWT = 6-minute walk test; ALP = alkaline phosphatase; CDR = CADTH Common Drug Review; FPS-R = Faces Pain Scale – Revised; PTH = parathyroid hormone; LLN = lower limit of normal; NA = not applicable; PHEX = phosphate-regulating endopeptidase homolog, X-linked; PROMIS = Patient-Reported Outcomes Measurement Information System; PTH = parathyroid hormone; RCT = randomized controlled trial; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SC = subcutaneous; SF-10 - Short Form (10) Health Survey for Children; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; TRP = tubular reabsorption of phosphate; ULN = upper limit of normal; XLH = X-linked hypophosphatemia.

Note: Three additional reports were included (CDR submission,[21] Health Canada reviewer's report,[8] and the FDA multi-discipline review[2]).

Source: Imel et al.,[30] Clinical Study Report for Study CL301.[13]

Table 5: Details of Studies CL201 and CL205

		Study CL201	Study CL205
DESIGNS AND POPULATIONS	**Study design**	Phase II, randomized, open-label, dose-finding study	Phase II, open-label, single-arm study
	Locations	France, Netherlands, the UK, and the US	The US
	Randomized (N)	52	13
	Inclusion criteria	• Children between 5 years and 12 years of age with open growth plates • Tanner stage of 2 or less based on breast and testicular development (with stages ranging from 1 to 5 where higher stages indicate more advanced pubertal development) • Diagnosis of XLH supported by 1 of the following: ○ Confirmed PHEX mutation in the patient or in a directly related family member with appropriate X-linked inheritance ○ Serum FGF23 level > 30 pg/mL by Kainos assay • Fasting serum phosphorus ≤ 0.904 mmol/L	• Male or female, aged 1 year to < 5 years • PHEX mutation or VUS in either the patient or in a directly related family member with appropriate X-linked inheritance • Biochemical findings associated with XLH, including serum phosphorus < 3.0 mg/dL and serum creatinine within age-adjusted normal range • Radiographic evidence of rickets; at least 5 patients had to have an RSS at the knee of at least 1.5 points as determined by central read

		Study CL201	Study CL205
		• Standing height < 50th percentile for age and gender using local normative data • Radiographic evidence of active bone disease, including rickets in the wrists and/or knees, and/or femoral or tibial bowing After the initial 36 patients were enrolled, another 16 patients were enrolled. The 16 additional patients were required to have an RSS of at least 1.5 at the knee.	
	Exclusion criteria	• Use of vitamin D metabolites or analogues within 14 days before second screening visit 2; washout took place during the screening period • Use of oral phosphate within 7 days prior to the second screening visit; washout took place during the screening period • Use of calcimimetics, aluminum hydroxide antacids, systemic corticosteroids, or thiazides within 7 days prior to the first screening visit • Use of growth hormone therapy within 3 months before first screening visit • Use of bisphosphonates for 6 months or more in the 2 years prior to the first screening visit • Presence of nephrocalcinosis on renal ultrasound graded ≥ 3 (defined as uniformly intense echoes throughout the pyramid; grade 4 is defined as stone formation: solitary focus of echoes at the tip of the pyramid) • Planned or recommended orthopedic surgery, including staples, 8-plates, or osteotomy within the clinical trial period • Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits • Evidence of tertiary hyperparathyroidism as determined by the investigator • Use of medication to suppress PTH (e.g., cinacalcet, calcimimetics) within 2 months prior to the first screening visit	• Unwilling to stop treatment with oral phosphate and/or pharmacologic vitamin D metabolite or analogue (e.g., calcitriol, alfacalcidol) during the screening period and for the duration of the study • Presence of nephrocalcinosis on renal ultrasound grade 4 (defined as stone formation: solitary focus of echoes at the tip of the pyramid) • Planned or recommended orthopedic surgery, including staples, 8-plates, or osteotomy, within the study period • Hypocalcemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits
DRUGS	**Intervention**	Initial doses of burosumab SC injection were 0.1 mg/kg, 0.2 mg/kg, or 0.3 mg/kg every two weeks. Subsequent doses were adjusted every 4 weeks in 0.3 mg/kg increments, as needed, based on 2-week post-dose (peak) fasting serum phosphorus levels. The target peak fasting serum phosphorus level was 1.13 mg/kg to 1.62 mmol/L.	The starting dose of burosumab SC injection was 0.8 mg/kg every two weeks, which could be increased to 1.2 mg/kg.
	Comparator(s)	Initial doses of burosumab SC injection were 0.2 mg/kg, 0.4 mg/kg, or 0.6 mg/kg every four weeks. Subsequent doses were adjusted every 4 weeks in 0.3 mg/kg increments, as needed, based on 2-week post-dose (peak) fasting serum phosphorus levels.	None

		Study CL201	Study CL205
		The target peak fasting serum phosphorus was 1.13 mmol/L to 1.62 mmol/L.	
DURATION	**Phase**		
	Open-label	Titration period: 16 weeks Treatment period: 48 weeks	64 weeks
	Follow-up	NA	12 weeks
	Extension	96 weeks	NA
OUTCOMES	**Primary end point**	Change from baseline in severity of rickets as measured by RSS total score	Change from baseline in serum phosphorus at week 40
	Secondary and exploratory end points	**Secondary:** • Change from baseline in severity of rickets as measured by RSS knee and wrist scores • Change from baseline in the radiographic appearance of rickets and bowing as measured by RGI-C global, knee, wrist, and long leg scores • Standing height, sitting height, arm length, and leg length • 6MWT • POSNA-PODCI • Serum phosphorus • Serum $1,25(OH)_2D$ • TmP/GFR • TRP • ALP • BALP • Serum iPTH **Exploratory:** • BOT-2 • SF-10	**Secondary:** • Change in rickets as assessed by the RGI-C global score at week 40 and week 64 • Change from baseline in RSS total score at week 40 and week 64 • Change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as determined by the RGI-C long leg score at week 40 and week 64 • Change in recumbent length/standing height from baseline to post-treatment study time points in cm, height-for-age z scores, and percentiles based on age and gender • Change and percentage change from baseline over time in serum ALP • Change from baseline over time in serum $1,25(OH)_2D$ and urinary phosphorus • Change in rickets as assessed by RGI-C wrist score and knee score at week 40 and week 64 • Change from baseline in RSS wrist score and knee score at week 40 and week 64
NOTES	**Publications**	Carpenter et al.[31]	Whyte et al.[32]

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; 6MWT = 6-minute walk test; ALP = alkaline phosphatase; BALP = bone-specific alkaline phosphatase; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency – Second Edition; CDR = CADTH Common Drug Review; FGF23 = fibroblast growth factor 23; iPTH = intact parathyroid hormone; PHEX = phosphate-regulating endopeptidase homolog, X-linked; POSNA = Pediatric Orthopaedic Society of North America; PODCI = Pediatric Outcomes Data Collection Instrument; PTH = parathyroid hormone; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SC = subcutaneous; SF-10 - Short Form (10) Health Survey for Children; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; TRP = tubular reabsorption of phosphate; VUS = variant of uncertain significance; XLH = X-linked hypophosphatemia.

Note: Three additional reports were included (CDR Submission,[21] Health Canada reviewer's report,[8] and the FDA multi-discipline review[2]).

Source: Carpenter et al.,[31] Whyte et al.,[32] Clinical Study Reports for studies CL201 and CL205.[10,11]

Table 6: Details of Study CL303

		Study CL303
DESIGNS AND POPULATIONS	**Study design**	Phase III, double-blind, placebo-controlled RCT
	Locations	France, Ireland, Italy, Japan, South Korea, the UK, and the US
	Randomized (N)	134
	Inclusion criteria	• Male or female, aged 18 years to 65 years, inclusive • Diagnosis of XLH supported by classic clinical features of adult XLH (such as short stature or bowed legs) and at least 1 of the following at screening: ○ documented PHEX mutation in either the patient or in a directly related family member with appropriate X-linked inheritance ○ serum intact fibroblast growth factor 23 level > 30 pg/mL by Kainos assay • Biochemical findings consistent with XLH at the second screening visit following overnight fasting (minimum 8 hours): ○ serum phosphorus < 0.81 mmol/L ○ ratio of renal tubular maximum phosphate reabsorption rate to GFR of < 2.5 mg/dL • Presence of skeletal pain attributed to XLH or osteomalacia, as defined by a score of ≥ 4 on BPI worst pain at the first screening visit • 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 • If taking chronic pain medications (including narcotic pain medications or opioids), must have been on a stable regimen for at least 21 days prior to the first screening visit and willing to maintain medications at the same stable dose(s) and schedule throughout the placebo-controlled treatment period of the study. The dose must not have exceeded 60 mg oral morphine equivalents/day.
	Exclusion criteria	• Use of a pharmacologic vitamin D metabolite or analogue (calcitriol, doxercalciferol, or paricalcitol) within 14 days prior to the second screening visit • Use of oral phosphate within 14 days prior to the second screening visit • Use of aluminum hydroxide antacids, acetazolamides, and thiazides within 7 days prior to the second screening visit • Chronic use of systemic corticosteroids, defined as more than 10 days in the 2 months prior to the first screening visit • Corrected serum calcium level ≥ 2.7 mmol/L at the second screening visit • Serum intact PTH ≥ 2.5 × ULN at the first screening visit • Use of medication to suppress PTH (cinacalcet, for example) within 60 days prior to the first screening visit • Use of bisphosphonates in the 2 years prior to the first screening visit • Use of denosumab in the 6 months prior to the first screening visit • Use of teriparatide in the 2 months prior to the first screening visit • Planned or recommended orthopedic surgery within the first 24 weeks of the clinical trial period • Use of burosumab, or any other therapeutic monoclonal antibody, within 90 days prior to the first screening visit • History of recurrent infection (other than dental abscesses, which are known to be associated with XLH) or predisposition to infection, or known immunodeficiency
DRUGS	**Intervention**	1 mg/kg (rounded to the nearest 10 mg) every 4 weeks
	Comparator(s)	Placebo

		Study CL303
Duration	**Phase**	
	Double-blind	24 weeks
	Open-label Extension	125 weeks for US patients and 72 weeks for other patients
Outcomes	**Primary end point**	Proportion of patients achieving mean serum phosphorus levels above the LLN
	Secondary and exploratory end points	**Secondary:** • Change from baseline to week 24 in BPI worst pain score • Change from baseline to week 24 in the stiffness score of the WOMAC • Change from baseline to week 24 in the physical function score of the WOMAC • Change from baseline to post-baseline visits in BPI pain severity score • Change from baseline to post-baseline visits in BPI pain interference score • Change from baseline to post-baseline visits in BFI worst fatigue score • Change from baseline to post-baseline visits in BFI global fatigue score • Change and percentage change from baseline to post-baseline visits in BALP • Change and percentage change from baseline to post-baseline visits in serum phosphorus, serum $1,25(OH)_2D$, TmP/GFR, and TRP **Exploratory:** • The number of active pseudofractures and/or fractures, as defined by skeletal survey at baseline, and the number and percentage of the baseline active pseudofractures and/or fractures that were healed, partially healed, unchanged, or worsened at post-baseline visits • The number of patients with baseline active pseudofractures and/or fractures and the number of those patients with changes from baseline to healed, partially healed, unchanged, or worsened at post-baseline visits • Change from baseline to post-baseline visits in 6MWT total distance walked (m) • Change from baseline to post-baseline visits in 6MWT percentage predicted distance based on published normative data
Notes	**Publications**	Insogna et al.[33]

6MWT = 6-minute walk test; BALP = bone-specific alkaline phosphatase; BFI = Brief Fatigue Inventory; BPI = Brief Pain Inventory; GFR = glomerular filtration rate; LLN = lower limit of normal; PHEX = phosphate-regulating endopeptidase homolog, X-linked; PTH = parathyroid hormone; RCT = randomized controlled trial; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; TRP = tubular reabsorption of phosphate; ULN = upper limit of normal; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; XLH = X-linked hypophosphatemia.

Note: Three additional reports were included (CDR submission,[21] Health Canada reviewer's report,[8] and the FDA multi-discipline review[2]).

Source: Insogna et al.,[33] Portale et al.,[34] Clinical Study Report for Study CL303.[12]

Description of Studies

A total of four studies met the inclusion criteria (Study CL301, Study CL201, Study CL205, and Study CL303).

Study CL301 (N = 61) was a multi-centre, randomized, open-label, phase III study comparing the efficacy and safety of burosumab to active control (oral phosphate and active vitamin D therapy) in children (one year to ≤ 12 years of age) with clinical evidence consistent with XLH and a confirmed PHEX mutation (in the patient or a direct relative) or variants of unknown significance. The study consisted of a screening visit, a treatment period of 64 weeks, and a treatment extension period of 76 weeks for patients in Europe, the US, Canada, and Australia. Eligible patients were randomized in a 1:1 ratio to receive either open-label burosumab (administered by SC injection) every two weeks or phosphate and active vitamin D therapy (administered orally) daily for a total of 64 weeks. Eligible

patients discontinued oral phosphate and active vitamin D therapy for seven days prior to randomization. Patients randomized to burosumab treatment remained off of oral phosphate and active vitamin D therapy throughout the duration of the study. Patients assigned to the burosumab treatment group received burosumab at a starting dose of 0.8 mg/kg every two weeks. The dose could be increased to 1.2 mg/kg every two weeks based on fasting serum phosphorus concentrations. Patients randomized to treatment with active control typically received multiple daily doses of oral phosphate and active vitamin D. Because of the variability in the doses and dosing frequencies of oral phosphates and active vitamin D therapies in clinical practice, these treatments were individualized for each patient at the investigator's discretion. Randomization was stratified by baseline rickets severity (RSS total score ≤ 2.5 versus > 2.5), age (< five years versus ≥ five years), and region (Japan versus the rest of world). At least 20 patients aged one year to under five years were planned to be included (approximately 10 in each treatment group), and no more than 10 patients aged one year to under three years of age were planned to be enrolled. To ensure appropriate gender distribution for the X-linked dominant disease, no more than 70% female patients were planned for enrolment.

Study CL201 (N = 52) was a randomized, multi-centre, open-label, dose-finding, phase II study to assess the efficacy and safety of burosumab in prepubescent children (five years to 12 years old) with XLH. The study consisted of two screening visits, a 16-week individual dose titration period, a 48-week treatment period, and a 96-week treatment extension period. The study initially enrolled 36 pediatric patients with XLH and radiographic evidence of bone disease. The study was expanded per Amendment 3 of the protocol to include additional patients. These were required to have an RSS of at least 1.5 points at the knee. The result was a total of approximately 50 patients expected overall. Potential patients were screened at an initial visit. Once the diagnosis of XLH and radiographic evidence of active bone disease (or an RSS of at least 1.5 points at the knee) were confirmed, patients discontinued oral phosphate and vitamin D metabolite therapy prior to randomization and throughout the duration of the study. Patients who successfully passed the initial screening requirements returned for a second screening visit a minimum of 14 days after vitamin D metabolite treatment had been stopped and a minimum of seven days after oral phosphate treatment had been stopped; the remaining screening assessments to confirm eligibility were performed. The baseline visit (week 0) could occur up to seven days after the second screening visit. Patients were enrolled sequentially into cohorts defined by the initial dose of burosumab; within each dose cohort, patients were randomized to a once-every-two-weeks or a once-every-four-weeks regimen. The monthly dose of burosumab was the same for the once-every-two-weeks regimen or the once-every-four-weeks regimen within each dose cohort:

- Dose cohort 1 received initial doses of 0.1 mg/kg every two weeks or 0.2 mg/kg every four weeks.
- Dose cohort 2 received initial doses of 0.2 mg/kg every two weeks or 0.4 mg/kg every four weeks.
- Dose cohort 3 received initial doses of 0.3 mg/kg every two weeks or 0.6 mg/kg every four weeks.

Patients were randomized 1:1 to every-two-weeks regimens or every-four-weeks regimens within each cohort; randomization was stratified by sex. The 16-week titration period (week 0 [baseline] to week 16) was intended to identify the burosumab dose required to achieve the target peak pharmacodynamic effect, based on serum phosphorus levels. The target fasting serum phosphorus range was 1.13 mmol/L to 1.62 mmol/L. The dose was adjusted

every four weeks, as needed, based on two-week post-dose (peak) fasting serum phosphorus levels. The dose was adjusted, if necessary, in 0.3 mg/kg increments. If the serum phosphorus level was rising, but had not yet reached the acceptable target range by the end of the titration period, titration continued into the treatment period, provided there were no safety concerns. In the treatment period (week 16 to week 64), patients continued on the every-two-weeks regimen or every-four-weeks regimen to which they had been randomized. Patients either continued to receive the individually optimized dose of burosumab established during the titration period or continued with dose titration. Only results from the every-two-weeks arm are reported in this review.

Study CL205 (N = 13) was a multi-centre, open-label, phase II study in children aged one year to four years with XLH who were naive to therapy or had previously received standard therapy with oral phosphate and active vitamin D. The goal was to assess the safety and efficacy of burosumab administered through SC injections every two weeks for a total of 64 weeks. To maintain gender balance, no more than 70% of patients could be the same sex. Patients receiving oral phosphate and active vitamin D therapy discontinued treatment during screening and for the duration of the study. All patients received burosumab at a starting dose of 0.8 mg/kg every two weeks. The dose could be increased to 1.2 mg/kg at any time during the study if a patient met the dose-adjustment criteria. Results were available up to week 40.

Study CL303 (N = 134) was a randomized, double-blind, placebo-controlled, multi-centre, phase III study that evaluated the efficacy and safety of burosumab in adult patients with XLH. No more than 70% female patients were planned for enrolment. Study CL303 comprised two screening visits, a baseline visit, a placebo-controlled treatment period (24 weeks), an open-label treatment continuation period (24 weeks), and an open-label treatment extension period (101 weeks for US patients and 48 weeks for other patients). Patients who met the initial screening requirements returned for a second screening visit to complete the remaining screening assessments and confirm eligibility. Potential patients receiving supplementation therapy with oral phosphate and active vitamin D metabolites or analogues discontinued treatment after the initial screening visit. The second screening visit occurred a minimum of 14 days after oral phosphate and vitamin D metabolite treatment had been stopped. Eligible patients were randomized in a 1:1 ratio to receive burosumab 1 mg/kg (rounded to the nearest 10 mg) or placebo administered SC every four weeks for 24 weeks during the placebo-controlled treatment period. Randomization was stratified by pain intensity and by region: North America, the European Union, Japan, and South Korea. After completing the placebo-controlled treatment period assessments at week 24, patients randomized to the placebo group began treatment with open-label burosumab at 1 mg/kg SC every four weeks for an additional 24 weeks (until week 48) in the treatment continuation period. All patients then continued burosumab treatment (on the same dosing regimen) in the open-label treatment extension period.

Populations

Inclusion and Exclusion Criteria

Patients enrolled in the CL301 study were children (one year to ≤ 12 years of age) with hypophosphatemia, radiographic evidence of rickets (RSS total score ≥ 2.0 points), and mutation or variant of uncertain significance in PHEX in either the patient or in a directly related family member with appropriate X-linked inheritance. Patients also were required to have open epiphyses and to have received oral phosphate and active vitamin D therapy for at least 12 consecutive months (for children ≥ three years of age) or at least six consecutive

months (for children < three years of age). Patients were excluded from the CL301 study if their height was above 50th percentile for age and sex based on country-specific norms, if they had a Tanner stage of at least 4, had used growth hormone therapy in the 12 months before screening, were planning orthopedic surgery, had renal ultrasound indicating nephrocalcinosis of grade 4 (on a scale of 0 to 4), had hypocalcemia or hypercalcemia, or their plasma PTH was greater than 19 pmol/L.

Study CL201 enrolled children between five years and 12 years of age with a diagnosis of XLH whose pubertal stage was classified as Tanner stage 2 or lower, and who had radiographic evidence of active bone disease, including rickets in the wrists and/or knees, and/or bowing of the femur or tibia. XLH was confirmed either by confirmed PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance or by a serum FGF-23 level of more than 30 pg per millilitre. In addition, patients had to have a fasting serum phosphorus level of 0.90 mmol per litre or less and a standing height less than the 50th percentile for age and sex using local normative data. Patients were excluded if they had used oral phosphate supplements, systemic glucocorticoids, aluminum hydroxide antacids, or thiazide diuretics within seven days prior to screening, had used vitamin D metabolites or analogues within 14 days prior to screening, or had used growth hormone therapy within three months prior to screening. Patients were excluded if they had hypocalcemia, hypercalcemia, nephrocalcinosis of grade 3 or higher as assessed by renal ultrasound, evidence of tertiary hyperparathyroidism as determined by the investigator, or if they had used calcimimetic drugs within two months before screening.

Study CL205 enrolled pediatric patients between one year and four years of age (inclusive) with hypophosphatemia and radiographic evidence of rickets (at least five patients with an RSS at the knee of at least 1.5 points at screening) and a confirmed PHEX mutation or variant of uncertain significance in either the patient or a directly related family member with appropriate X-linked inheritance. In addition, patients had to have a fasting serum phosphorus concentration of less than 0·97 mmol/L and serum creatinine within the age-adjusted normal range. Patients were excluded if they had nephrocalcinosis of grade 4 as assessed by renal ultrasound, if they had planned or been recommended for orthopedic surgery, and if they had hypocalcemia or hypercalcemia.

Study CL303 enrolled adult patients between 18 years and 65 years of age with bone or joint pain at baseline and a diagnosis of XLH supported by clinical and biochemical features consistent with XLH and/or a confirmed PHEX mutation (self or family member consistent with X-linked inheritance). If the patient was receiving chronic pain medications, they had to have been on a stable regimen for at least 21 days prior to screening and be willing to maintain medications at the same stable dose (maximum of 60 mg oral morphine equivalents/day). Patients were excluded if they used vitamin D metabolite or analogue or oral phosphate within 14 days prior to screening, if they used aluminum hydroxide antacids, acetazolamides, or thiazides within seven days prior to screening, if they used medication to suppress PTH within 60 days before screening, and if they had a planned or recommended orthopedic surgery, corrected serum calcium greater than or equal to 2.7 mmol/L, serum intact PTH ≥ 2.5-fold the upper limit of normal (ULN), or traumatic fracture or orthopedic surgery within six months prior to screening.

Baseline Characteristics

In Study CL301, baseline characteristics were generally similar between groups (Table 7 and Table 8). All patients enrolled showed signs of XLH disease at baseline by the presence of rickets (RSS total score ≥ 2.0), metaphyseal abnormalities on knee and wrist

radiographs, and serum phosphorus concentrations of less than 0.97 mmol/L. (The lower limit of the reference range for pediatric patients is 1.03 mmol/L.) Most patients were positive for pathogenic mutations in the PHEX gene (55 out of 61 [90%]). Most patients had a history of bowing in the tibia or fibula (84%), bowing in the femur (80%), and/or intoeing (57%). All patients had received conventional therapy with oral phosphate and active vitamin D analogues before enrolling in the study, with a mean duration of conventional therapy before entering the study of 3.8 (SD = 3.09) years. Conventional therapy was initiated within the first two years of life for 64% of patients (39 out of 61). Patients' growth was substantially impaired, where the mean standing height as percentile for age and gender was 5.8% (SD = 9.65%; range: 0% to 45%) with a median z score for height of −2.18 (range: −5.0 to −0.1). This indicates that more than half of the patients had short stature (given that children who are growing and developing normally would generally be on or between z scores of −2 and 2).[35]

In Study CL201, all patients enrolled in the burosumab-every-two-weeks arm presented with signs of XLH disease at baseline by different measures (Table 7 and Table 8). Baseline radiographs showed the presence of rickets (score > 0) in the majority of patients at the wrists (76.9%), at the knees (92.3%), and overall (96.2%). Metaphyseal abnormalities were noted on knee and wrist radiographs in the majority of patients. The majority of patients (92.3%) had been diagnosed at some point with bowing in the limbs. Nearly all patients (92.3%) had received conventional therapy with oral phosphate and active vitamin D analogues before enrolling in the study, with a mean duration of conventional therapy before entering the study of 7.02 (SD = 2.14) years. Conventional therapy had been initiated for approximately half of the patients within their first two years of life. Most patients were positive for pathogenic mutations in the PHEX gene (88.5%). Patients' growth was substantially impaired, with a mean standing height as percentile for age and gender of 11.13% (SD = 13.80%; range: 0% to 47.7%) and a mean Z score of −1.72 (SD = 1.03; range: −4.0 to −0.1).

In Study CL205, most patients (84.6%) were positive for known pathogenic mutations in the PHEX gene. The mean serum phosphorus concentration was 0.81 (SD = 0.092) mmol/L, below the lower limit of the reference range for pediatric patients (1.03 mmol/L) (Table 7 and Table 9). All patients (100%) had received conventional therapy with oral phosphate and active vitamin D analogues before enrolling in the study. The mean duration of conventional therapy before entering the study was 16.9 (SD = 14.39) months, with a mean age at initiation of 20.9 (SD = 18.17) months. The baseline radiographs showed the presence of rickets (score > 0) in all patients at both the knees and wrists. The mean RSS total score was 2.92 (SD = 1.367). Metaphyseal abnormalities were noted on radiographs in all patients at the distal femur and in most patients at the proximal tibia, the distal ulna, and the distal radius. Alkaline phosphatase (ALP) was elevated in 84.6% of patients, with a mean of 549 (SD = 193.8) U/L (approximately 297 U/L to 345 U/L, depending on the age and sex of the child). Growth was impaired at baseline, with a mean recumbent length or standing height 89.15 (SD = 7.597) cm, a mean percentile for age and sex of 18.0% (SD = 25.26%), and a mean z score of –1.38 (SD = 1.195).

In Study CL303, the mean times since XLH diagnosis were similar in both treatment groups, with a mean time of 31.4 (SD = 15.60) years for the study population. Overall, 94.8% of patients had PHEX mutations, classified as either pathogenic, likely pathogenic, or variants of uncertain significance. At baseline, serum phosphorus concentration, TmP/GFR, and serum $1,25(OH)_2D$ concentration were similar between the burosumab and placebo groups. The majority of patients (71.6%) had a BPI average pain score greater

than 6.0. Approximately 67.9% of patients were receiving pain medication at baseline. The majority of patients (67.2%) were receiving non-opioid pain medications; 22.4% of patients were receiving opioids. Baseline radiographic characteristics were generally similar between the treatment groups. Most patients (94.0%) had bowing, which was common in both the upper extremities (87.3% of patients) and lower extremities (85.8% of patients). Overall, 68.7% of patients had undergone orthopedic surgery, most commonly osteotomy. Enthesopathy was present in nearly all patients (99.3%) at baseline. A substantial percentage of patients had evidence of prior fractures, healed (i.e., non-active) fractures (59.0%), or pseudofractures (34.3%) at baseline. Also, a large percentage of patients had active pseudofractures (47.0%) or active (i.e., unhealed) fractures (11.9%). Overall, 63.4% of patients had a reported history of osteoarthritis (Table 10).

Table 7: Summary of Baseline Characteristics in Studies CL301, CL201, and CL205

	Study CL301		Study CL201	Study CL205
Baseline characteristics	**Burosumab every two weeks (N = 29)**	**Phosphate and active vitamin D (N = 32)**	**Burosumab every two weeks (N = 26)**	**Burosumab every two weeks (N = 13)**
Age (years)				
Mean (SD)	5.83 (3.426)	6.34 (3.244)	8.7 (1.72)	2.94 (1.146)
Median (range)	5.80 (0.8 to 12.8)	6.20 (1.2 to 11.9)	9.0 (5 to 12)	2.80 (1.2 to 4.9)
Sex, n (%)				
Male	13 (44.8)	14 (43.8)	12 (46.2)	9 (69.2)
Female	16 (55.2)	18 (56.3)	14 (53.8)	4 (30.8)
Race, n (%)				
White	25 (86.2)	25 (78.1)	23 (88.5)	12 (92.3)
Asian	2 (6.9)	6 (18.8)	0	0
Black or African-American	0	0	2 (7.7)	1 (7.7)
Other	2 (6.9)	1 (3.1)	1 (3.8)	0
Body weight (kg)				
Mean (SD)	19.59 (8.984)	21.55 (8.910)	31.87 (7.918)	12.92 (1.816)
Median (range)	17.0 (9.0 to 43.5)	20.15 (9.0 to 41.5)	33.05 (17.6 to 48.4)	13.00 (9.2 to 15.6)
Standing height or recumbent length (percentile for age and gender)				
Mean (SD)	5.87 (9.976)[a]	5.74 (9.505)	11.13 (13.798)	18.044 (25.26)
Median (range)	1.08 (0.0 to 40.1)[a]	1.72 (0.0 to 45.0)	4.28 (0.0 to 47.7)	8.519 (0.01 to 83.29)
Standing height or recumbent length (z score)				
Mean (SD)	−2.32 (1.167)[b]	−2.05 (0.868)	−1.72 (1.026)	−1.378 (1.195)
Median (range)	−2.30 (−5.0 to −0.3)[b]	−2.12 (−4.7 to −0.1)	−1.72 (−4.0 to −0.1)	−1.371 (−3.66 to 0.97)
Renal ultrasound score (0 – 5 scale) – n (%)				
0	24 (82.8)	23 (71.9)	17 (65.4)	13 (100)
1	2 (6.9)	3 (9.4)	6 (23.1)	0
2	2 (6.9)	3 (9.4)	3 (11.5)	0
3	1 (3.4)	3 (9.4)	0	0
PHEX mutation result				
Positive	27 (93.1)	28 (87.5)	23 (88.5)	11 (84.6)

Baseline characteristics	Study CL301		Study CL201	Study CL205
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
Likely pathogenic variant	2 (6.9)	1 (3.1)	1 (3.8)	1 (7.7)
Variant of unknown significance	0 (0.0)	2 (6.3)	1 (3.8)	1 (7.7)
Negative	0 (0.0)	1 (3.1)	1 (3.8)	0
Number (%) of patients who received prior conventional therapy – n (%)	29 (100.0)	32 (100.0)	24 (92.3)	12 (92.3)
Duration of prior conventional therapy in years				
Mean (SD)	3.31 (3.118)[c]	4.31 (3.031)[c]	7.02 (2.138)[c]	1.39 (1.20)
Median (range)	2.19 (0.5 to 12.2)	3.45 (0.8 to 12.0)	7.06 (3.1 to 10.9)	1.08 (0.09 to 3.36)
Age when conventional therapy was initiated in years				
Mean (SD)	2.61 (2.555)	2.07 (2.032)	2.21 (1.458)	1.74 (1.51)
Median (range)	1.90 (0.1 to 11.3)	1.50 (0.0 to 6.5)	2.15 (0.0 to 5.7)	1.05 (0.12 to 4.49)
Serum phosphorus (mmol/L)				
n	29	32	26	13
Mean (SD)	0.78 (0.077)	0.74 (0.082)	0.77 (0.131)	0.81 (0.092)
Median (range)	0.79 (0.7 to 0.9)	0.74 (0.6 to 0.9)	0.74 (0.6 to 1.1)	0.810 (0.65 to 0.94)
TmP/GFR (mmol/L)				
n	24	30	25	NR
Mean (SD)	0.708 (0.1206)	0.649 (0.1066)	0.70 (0.159)	NR
Median (range)	0.698 (0.44 to 0.95)	0.646 (0.36 to 0.88)	0.72 (0.5 to 1.1)	NR
Serum $1,25(OH)_2D$ (pmol/L)				
n	28	30	26	12
Mean (SD)	110.36 (48.106)	96.42 (35.729)	107.34 (57.115)	116.58 (45.811)
Median (range)	94.65 (37.0 to 198.7)	94.20 (31.2 to 184.6)	90.61 (42.1 to 259.2)	108.00 (60.0 to 211.0)
RSS total score				
Mean (SD)	3.17 (0.975)	3.19 (1.141)	1.92 (1.172)	2.92 (1.367)
Median (range)	3.00 (2.0 to 6.5)	3.00 (2.0 to 6.5)	(0.0 to 4.5)	3.00 (1.0 to 6.5)
≤ 2.5	10 (34.5)	12 (37.5)	NR	NR
> 2.5	19 (65.5)	20 (62.5)	NR	NR
Total score > 0, n (%)	29 (100)	32 (100)	25 (96.2)	NR
RSS wrist score				
Mean (SD)	1.48 (0.661)	1.45 (0.807)	0.71 (0.619)	1.27 (0.696)
Median (range)	1.50 (0.5 to 3.5)	1.25 (0.0 to 3.5)	0.50 (0.0 to 2.5)	1.50 (0.5 to 2.5)
Wrist score > 0, n (%)	29 (100)	32 (100)	20 (76.9)	NR
RSS knee score				
Mean (SD)	1.69 (0.507)	1.73 (0.595)	1.21 (0.681)	1.65 (0.801)
Median (range)	1.50 (1.0 to 3.0)	1.50 (1.0 to 4.0)	1.50 (0.0 to 2.0)	1.50 (0.5 to 4.0)
Knee score > 0, n (%)	29 (100)	32 (100)	24 (92.3)	NR

Baseline characteristics	Study CL301		Study CL201	Study CL205
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
Knee score ≥ 1.5, n (%)	NR	NR	15 (57.7)	NR
Serum ALP concentration (U/L)				
Mean (SD)	510.8 (124.9)	523.4 (154.42)	461.9 (110.21)	548.5 (193.80)
Median (range)	481.0 (295 to 768)	508.5 (365 to 1,179)	469.5 (280 to 706)	506.0 (286 to 980)

1,25(OH)2D = 1,25-dihydroxyvitamin D; ALP = alkaline phosphatase; PHEX = phosphate-regulating endopeptidase homolog, X-linked; RSS = Rickets Severity Score; SD = standard deviation; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; XLH = X-linked hypophosphatemia.

[a] One patient in the burosumab group was [redacted] old at the screening visit and was [redacted], [redacted] old when [redacted] received the first dose of study drug.

[b] Baseline data were not available for one patient in the burosumab group.

[c] Conventional therapy was defined as any of the following standardized medication names: Alfacalcidol, Calcitriol, Calcifediol, K-Phos Neutral, Neutra-Phos-K, Neutra-Phos, Phos-Nak, Phosphoneurol, Phosphorus, Polyfusor Phosphat, Sodium Phosphate, Sodium Phosphate Dibasic.

Source: Clinical Study Reports for studies CL301, CL201, and CL205.[10,11,13]

Table 8: X-Linked Hypophosphatemia Medical History in Studies CL301 and CL201

Baseline characteristics	Study CL301		Study CL201
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)
XLH medical history			
Bowing of the legs, tibia or fibula	24 (82.8)	27 (84.4)	NR
Bowing of the legs, femur	23 (79.3)	26 (81.3)	NR
Intoeing	14 (48.3)	21 (65.6)	16 (61.5)
Dental abscesses	10 (34.5)	11 (34.4)	16 (61.5)
Knock-knees	8 (27.6)	6 (18.8)	5 (19.2)
Joint stiffness (limited range of motion)	8 (27.6)	5 (15.6)	NR
Craniosynostosis	4 (13.8)	6 (18.8)	3 (11.5)
Excessive cavities	2 (6.9)	4 (12.5)	6 (23.1)
Chiari malformation	1 (3.4)	1 (3.1)	2 (7.7)
Any bowing in limbs[a]	NR	NR	24 (92.3)
Unusual gait or way of walking	NR	NR	20 (76.9)
Bowing of lower legs	NR	NR	16 (61.5)
Short stature/delayed growth	NR	NR	17 (65.4)
Bowing of upper legs	NR	NR	16 (61.5)
Delayed walking	NR	NR	9 (34.6)
Nephrocalcinosis	NR	NR	6 (23.1)
Widened/thickened wrists	NR	NR	4 (15.4)
Bowing of the forearms	NR	NR	2 (7.7)
Irregular shaped chest	NR	NR	3 (11.5)

Baseline characteristics	Study CL301		Study CL201
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)
Other	NR	NR	2 (7.7)
Impaired renal function[b]	NR	NR	1 (3.8)
Hearing loss	NR	NR	0 (0.0)

NR = not reported; GFR = glomerular filtration rate; XLH = X-linked hypophosphatemia.

[a] Any bowing in limbs was defined as a patient ever having been diagnosed with "bowing of the forearms," "knock-knees," "bowing of upper legs," "bowing of lower legs," or "intoeing."

[b] Impaired renal function had resolved for one patient at entry to the study; serum creatine was 0.5 mg/mL, and GFR was 140 mL/min/1.73 m^2 at baseline.

Source: Clinical Study Reports for studies CL301 and CL201.[10,13]

Table 9: Medical History Reported in at Least Three Patients by System Organ Class in Study CL205

System organ class preferred term	Burosumab every two weeks (N = 13)
	n (%)
Musculoskeletal and connective tissue disorders	12 (92.3)
Knee deformity	8 (61.5)
Bone deformity	7 (53.8)
Foot deformity	5 (38.5)
Arthralgia	3 (23.1)
Lordosis	3 (23.1)
Pam in extremity	3 (23.1)
Congenital, familial, and genetic disorders	11 (84.6)
Rickets familial hypophosphatemic	10 (76.9)
Skull malformation	7 (53.8)
Tibial torsion	6 (46.2)
Metaphyseal dysplasia	3 (23.1)
Gastrointestinal disorders	8 (61.5)
Constipation	4 (30.8)
Abdominal pain	3 (23.1)
Gastroesophageal reflux disease	3 (23.1)
Body height below normal	6 (46.2)
Gait disturbance	7 (53.8)
Tooth abscess	4 (30.8)
Seasonal allergy	3 (23.1)

Source: Clinical Study Report for Study CL205.[11]

Table 10: Summary of Baseline Characteristics in Study CL303

Baseline characteristics	CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Age (years)		
Mean (SD)	41.29 (11.582)	38.65 (12.756)
Range	20.0 to 63.4	18.5 to 65.5
Sex, n (%)		
Male	24 (35.3)	23 (34.8)
Female	44 (64.7)	43 (65.2)
Race, n (%)		
White	55 (80.9)	53 (80.3)
Asian	12 (17.6)	9 (13.6)
Black or African-American	0	3 (4.5)
Other	1 (1.5)	1 (1.5)
Body weight (kg)		
Mean (SD)	70.06 (19.004)	71.27 (18.892)
Range	37.1 to 139.6	36.1 to 126.6
Height (cm)[a]		
Mean (SD)	152.15 (9.491)	152.69 (11.836)
Range	126.2 to 176.0	120.6 to 175.0
Time since XLH diagnosis (years)		
n	39	42
Mean (SD)	31.47 (15.592)	31.36 (15.791)
Range	0.5 to 55.8	0.5 to 64.7
Orthopedic surgeries, n (%)	45 (66.2)	47 (71.2)
Osteoarthritis, n (%)	47 (69.1)	38 (57.6)
Nephrocalcinosis (calcium deposits in kidneys)	11 (16.2)	5 (7.6)
Nephrolithiasis (kidney stones)	10 (14.7)	8 (12.1)
Serum phosphorus (mmol/L), n	68	66
Mean (SD)	0.653 (0.1072)	0.617 (0.1001)
Median (range)	0.650 (0.40 to 1.00)	0.600 (0.40 to 0.80)
TmP/GFR (mg/dL), n		
n	66	64
Mean (SD)	1.68 (0.400)	1.60 (0.369)
Median (range)	1.63 (0.95 to 3.41)	1.61 (0.71 to 2.62)
Serum $1,25(OH)_2D$ (pg/mL), n		
n	66	64
Mean (SD)	32.4 (12.96)	33.5 (15.61)
Median (range)	32.5 (4 to 76)	30.0 (4 to 80)
Baseline BPI average pain		
Mean (SD)	5.14 (1.558)	5.05 (1.481)
Range	1.1 to 8.6	1.5 to 7.8
Category – n (%)		

Baseline characteristics	CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
≤ 6	46 (67.6)	49 (74.2)
> 6	22 (32.4)	17 (25.8)
Baseline BPI worst pain		
Mean (SD)	6.81 (1.308)	6.54 (1.433)
Range	3.0 to 8.9	3.1 to 9.1
Category – n (%)		
≤ 6	15 (22.1)	23 (34.8)
> 6	53 (77.9)	43 (65.2)
Any pain medication use at baseline, n (%)	47 (69.1)	44 (66.7)
Pain medication use at baseline by category, n (%)		
Opioids	17 (25.0)	13 (19.7)
Non-opioid pain medications[b]	47 (69.1)	43 (65.2)
Neuropathic pain medications/antidepressants	4 (5.9)	3 (4.5)
Other pain medications	7 (10.3)	1 (1.5)
Radiographic, n (%)		
Bowing (any location)	64 (94.1)	62 (93.9)
Bowing upper extremity (any location)	58 (85.3)	59 (89.4)
Bowing lower extremity (any location)	60 (88.2)	55 (83.3)
Enthesopathy (any location)	68 (100.0)	65 (98.5)
Active fractures (any location)	8 (11.8)	8 (12.1)
Non-active fractures (any location)	42 (61.8)	37 (56.1)
Active pseudofractures (any location)	29 (42.6)	34 (51.5)
Non-active pseudofractures (any location)	24 (35.3)	22 (33.3)
Phosphate/vitamin D metabolites or analogues, ever, n (%)		
Phosphate only	3 (4.4)	1(1.5)
Vitamin D metabolites or analogues only	3 (4.4)	3 (4.5)
Phosphate and vitamin D metabolites or analogues	59 (86.8)	62 (93.9)
No phosphate or vitamin D metabolites or analogues	3 (4.4)	0
PHEX mutation result, n (%)		
Pathogenic	45 (66.2)	50 (75.8)
Likely pathogenic	8 (11.8)	7 (10.6)
Variant of uncertain significance	9 (13.2)	8 (12.1)
Likely benign	0	0
No mutation	6 (8.8)	1 (1.5)

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; BPI = Brief Pain Inventory; PHEX = phosphate-regulating endopeptidase homolog, X-linked; SD = standard deviation; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; XLH = X-linked hypophosphatemia.

[a] n = 65 placebo; n = 67 burosumab.

[b] Non-opioid pain medication is defined as nonsteroidal anti-inflammatory drugs and acetaminophen.

Source: Clinical Study Report for Study CL303.[12]

Interventions

In Study CL301, patients randomized to receive burosumab began treatment with 0.8 mg/kg administered every two weeks by SC injection in the abdomen, upper arms, thighs, or buttocks; the injection site was rotated with each injection. The dose could be increased to 1.2 mg/kg every two weeks if a patient met the following dose-adjustment criteria: two consecutive serum phosphorus measurements were below the normal range; serum phosphorus concentrations had increased by less than or equal to 0.1615 mmol/L from baseline; and the patient had not missed a dose of burosumab that would account for the decrease in serum phosphorus concentration. The maximum allowable dose of burosumab per administration was 90 mg. For patients randomized to active control, oral phosphate and active vitamin D therapy was administered on an individualized basis at the discretion of the investigator. Calcitriol and alfacalcidol dosages were adjusted based on the clinical and laboratory values that guide best possible treatment. Trained personnel administered burosumab by SC injection or dispensed oral phosphates and active vitamin D treatment at the investigational site or during home health visits (burosumab treatment group only). No significant changes to a patient's diet or medication schedule (other than assigned study treatments) were to be made during the study unless medically indicated. Patients randomized to the burosumab group were prohibited from receiving oral phosphate and active vitamin D for the duration of the study. Patients randomized to the active-control group received oral phosphate and active vitamin D during the treatment period. The following medications were prohibited throughout the study period for both treatment groups: aluminum hydroxide antacids, systemic corticosteroids, acetazolamide, thiazides, growth hormone therapy, PTH suppressors, current or prior use of leuprorelin, triptorelin, goserelin, or other drugs known to delay puberty, and any therapeutic monoclonal antibody therapy.

In Study CL201, initial doses for dose cohorts one, two, and three for the once-every-two weeks regimen were 0.1 mg/kg, 0.2 mg/kg, and 0.3 mg/kg, respectively. The dose was adjusted as needed every four weeks in 0.3 mg/kg increments, based on two-week post-dose (peak) fasting serum phosphorus levels. Trained personnel administered the study drug through SC injection in the abdomen, upper arms, and thighs; the injection site was rotated with each injection.

In Study CL205, trained personnel administered the study drug by SC injection at the investigational site or during home health visits. Patients received burosumab at a starting dose of 0.8 mg/kg every two weeks. The dose could be increased to 1.2 mg/kg every two weeks at any time if a patient met the dose-adjustment criteria, which were similar to those applied in the CL301 study.

Throughout studies CL201 and CL205, no significant changes to patients' diets or medication schedules were allowed unless medically indicated. Investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except those specified as prohibited. The following medications remained prohibited throughout the conduct of the study: pharmacologic vitamin D metabolites or analogues, oral phosphate, aluminum hydroxide antacids, thiazides, adjunctive growth hormone, bisphosphonate therapy, chronic use of systemic corticosteroids, PTH suppressors, and any other monoclonal antibody therapy.

In the CL303 study, burosumab was supplied as a sterile, clear, colourless, preservative-free solution in single-use, 5 mL vials containing 1 mL of burosumab at a concentration of

30 mg/mL. Placebo was supplied as a sterile, clear, colourless, preservative-free solution in single-use, 5 mL vials containing 1 mL of placebo. The composition of the placebo solution was the same as that of the burosumab investigational product, but without the active substance. Placebo was prepared and administered in the same manner as burosumab. Patients randomized to receive burosumab began treatment with an SC injection of 1.0 mg/kg rounded to the nearest 10 mg, administered every four weeks (every 28 days). The amount of drug administered was calculated based on baseline body weight, up to a maximum dose of 90 mg. The dose remained fixed for the duration of the study, provided serum phosphorus levels did not exceed 1.61 mmol/L at any time or 1.45 mmol/L on two occasions, and body weight did not change by more than 20% from the baseline measurement. The dose was recalculated if body weight changed by more than 20%. If serum phosphorus increased to more than 1.61 mmol/L at any time, the patient treatment assignment was unblinded to the investigator (during the placebo-controlled treatment period) and the dose of burosumab was decreased by half. If serum phosphorus increased above the ULN (1.45 mmol/L), but did not exceed 1.61 mmol/L, the patient treatment assignment was unblinded (during the placebo-controlled treatment period) and the dose of burosumab decreased by half only if a second phosphorus result exceeded the ULN. Following a downward dose adjustment, the investigator, together with the sponsor's medical monitor, determined if, when, and how to up-titrate the dose. Trained personnel administered the study drug by SC injection in the abdomen, upper arms, or thighs; the injection site was rotated with each injection. A maximum of 1.5 mL was administered at a single injection site. If the dose required was greater than 1.5 mL, multiple injections were administered. Throughout the study, a patient's diet or medication schedule was not to change significantly unless medically indicated. Investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those specified as prohibited medications. The following medications remained prohibited throughout the conduct of the study: pharmacologic vitamin D metabolites or analogues, oral phosphate, aluminum hydroxide antacids, acetazolamides, thiazides, bisphosphonate therapy, denosumab therapy, teriparatide therapy, chronic use of systemic corticosteroids, PTH suppressors, and any other monoclonal antibody therapy.

Outcomes

Rickets Severity Score

RSS was constructed to measure rickets severity in the wrists and knees based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected.[36,37] RSS is a 10-point scale (4 points for the wrists and 6 points for the knees) where higher scores indicate greater severity of rickets. A score of 10 represents the most extreme degree of rickets severity, while a score of 0 indicates the absence of radiographic changes of rickets.[36,37] RSS has been validated in patients with nutritional rickets.[37] The inter-rater reliability of the RSS was evaluated in Study CL201, which was a phase II, randomized controlled trial of children with XLH. The Pearson correlation ranged from 0.83 to 0.89. The intra-rater reliability was excellent (Pearson correlation = 0.91). In the clinical trials of XLH, RSS was found to be statistically significantly correlated with clinical features of XLH, such as growth, walking ability, and self-reported pain and physical function.[37] An MCID for RSS total score was not identified from the literature.

In the CL301, CL201, and CL205 studies, for the assessment of RSS scores during treatment, radiographs of the wrists and knees from individual patients were presented in random order, with the radiologist blinded to patient identity, patient treatment status, and

the timing of the radiographs. To obtain the RSS score, the blinded radiologist was presented with bilateral radiographs of the wrists (or knees) and asked to choose the side considered to be the most severe. The radiologist then assigned an RSS wrist (or knee) score to the image deemed to be the more severe among the bilateral images. Therefore, the RSS score was the worst possible score for either side.

Change from baseline in severity of rickets as measured by RSS total score was a primary outcome in Study CL201 and a key secondary outcome in studies CL301 and CL205. Change from baseline in severity of rickets as measured by RSS knee and wrist scores were key secondary outcomes in Study CL201 and were other outcomes in studies CL301 and CL205. In addition, responder analyses were performed in all three studies for the RSS total score as follows: percentage of patients with an RSS total score reduction from baseline of at least 1.0 among patients with baseline RSS total score of at least 1.0 ("RSS responders"), and percentage of patients who healed completely among patients with a baseline of RSS total score greater than 0 ("complete RSS responders"). The sponsor indicated that, given that the variability of the RSS total score was 0.5, a difference of 1.0 would exceed the variability of the RSS total score.

Radiographic Global Impression of Change

The RGI-C scale was constructed to measure the change in severity of rickets as a complement to the RSS.[38] The RGI-C methodology allows for the evaluation of change in the radiographic appearance of rickets through a side-by-side comparison of two images — one taken earlier and one taken at a later time point.[10] It has been validated in patients with hypophosphatasia.[38] It is a 7-point change scale that provides an assessment of bone structure associated with the pathophysiology of hypophosphatasia. The changes from baseline in RGI-C scores are based on ratings of the characteristics of severe hypophosphatasia, including irregularity of the provisional zone of calcification; physeal widening; metaphyseal flaring, fraying, radiolucencies, and patchy osteosclerosis; altered ratio of mid-diaphyseal, cortex-to-bone thickness; gracile bones; absence of some or all bones; and recent fractures. For patients with rickets, a reduction of 3 points (recorded as "–3") represented severe worsening, and an increase of 3 points (recorded as "+3) indicated complete healing of the skeletal disease. For each patient, the mean score among the radiologists was used for analysis, with a response to treatment defined as a mean increase of 2 or more points (i.e., substantial healing). Inter-rater agreement was evaluated among pediatric radiologists in pediatric patients with hypophosphatasia. Good to moderate intra- and inter-rater agreement was achieved. RGI-C scores were found to be significantly associated with the RSS and with measures of global function, disability, endurance, and growth in patients aged six years to 12 years at baseline.[38] An MCID for the RGI-C score was not identified from the literature.

In studies CL301, CL201, and CL205, three pediatric radiologists not affiliated with the conduct of the study or the sponsor performed RGI-C ratings for the wrist, knee, and long leg radiographs. Prior to rating any radiographs, the three radiologists were trained to perform RGI-C ratings to gain consensus on the terminology used to describe XLH-related radiographic abnormalities and establish inter-rater reliability. The radiologists were blinded to treatment assignment and patient data. The ratings were performed independently using an electronic data capture system, with the radiologists having no opportunity to discuss images or compare ratings; ratings could not be retrieved or changed by the radiologists after submission. Radiograph pairs were presented for review in random order.

Change from baseline in the radiographic appearance of rickets as measured by RGI-C global score was the primary outcome in Study CL301 and a key secondary outcome in studies CL201 and CL205. Change in lower extremity skeletal abnormalities as assessed by the RGI-C long leg score was a key secondary outcome in studies CL301, CL201, and CL205. Change in rickets as assessed by RGI-C wrist and knee scores was a key secondary efficacy outcome in Study CL201 and another efficacy outcome in studies CL301 and CL205. The proportion of patients with a mean RGI-C global score greater than or equal to +2.0 (substantial healing) was another efficacy end point in Study CL301.

Growth

Short stature is one of the predominant features in children with XLH. Growth of the legs and trunk has been shown to be uncoupled in XLH and related to serum phosphate levels.[39] Growth is measured by changes in standing height or recumbent length (and percentiles) prior to and following treatment. Recumbent length is measured in patients less than two years old or who are unable or unwilling to stand for measurement. Growth was evaluated using age- and gender-adjusted z scores for standing height or recumbent length at the study visits at which height was measured. Growth velocity was calculated as the change in growth between intervals on an annualized basis. Growth, as measured by standing height or recumbent length, was evaluated on a percentile basis using clinical growth charts from the Centers for Disease Control and Prevention National Center for Health Statistics.[40] Children who are growing and developing normally would generally be on or between z scores of −2 and 2.[35]

Change from baseline in standing height or recumbent length z score was a secondary end point in studies CL301, CL201, and CL205. Change in growth velocity z score was a secondary efficacy end point in studies CL201 and CL205, and was another secondary end point in Study CL301.

Serum Phosphorus

Change from baseline in serum phosphorus was the primary efficacy end point in Study CL205 and a secondary end point in studies CL301 and CL201. The proportion of patients achieving the normal range of serum phosphorus (1.03 mmol/L to 1.97 mmol/L) was also reported in studies CL301, CL201, and CL205. In Study CL303, the primary end point was the proportion of patients achieving mean serum phosphorus levels above the LLN (0.81 mmol/L) at the midpoint of the dose interval (i.e., weeks 2, 6, 10, 14, 18, and 22), as averaged across dose cycles between baseline and week 24.

Serum 1,25-Dihydroxyvitamin D, TmP/GFR, TRP, ALP, BLP, and Serum iPTH

Change from baseline in ALP was a secondary end point in studies CL301, CL201, and CL205.

Change from baseline in bone-specific alkaline phosphatase (BALP) was a secondary end point in studies CL201 and CL303.

Change from baseline in $1,25(OH)_2D$ was a secondary end point in all of the included studies.

Change from baseline in TRP and in TmP/GFR were secondary end points in studies CL301, CL201, and CL303.

Brief Pain Inventory

The BPI is a questionnaire designed to provide information on pain intensity (the sensory dimension, four items) and the degree to which pain interferes with functioning in daily living (the reactive dimension, seven items). Four items assess the patient's pain intensity: pain at its worst in the last 24 hours; pain at its least in the last 24 hours; average pain; and pain right now, using a 0 to 10 numeric rating scale, with "0" representing "no pain" and "10" representing "pain as bad as you can imagine." For the seven items assessing pain interference with functioning, patients are asked to rate how their pain interferes with seven life domains — general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life — on a similar type of numeric rating scale. The anchor points in each item of the interference scale are "0" (not interfered) and "10" (completely interfered). The scores for the two BPI subscales (pain intensity and pain interference) range from 0 to 10 and are calculated using the mean of their corresponding items' scores. The total BPI score is the mean of the two subscale scores. A high score represents a high pain intensity or pain interference. It was originally developed to evaluate cancer pain (breast, prostate, colon, rectum, or gynecologic cancer). However, it has also been shown to be a reliable (e.g., in terms of internal consistency and test-retest reliability) and valid (e.g., in terms of construct, convergent, and discriminative validity) instrument for evaluating non-malignant chronic pain (e.g., low back pain, osteoarthritis, rheumatoid arthritis, or multiple sclerosis) across various languages. It is also commonly used for non-malignant pain.[41,42] An overall MCID for BPI has not been identified from the literature, although a two-point change was suggested by Mathias et al. as a reasonable estimate for the MCID of the BPI worst pain item in breast cancer patients with metastases.[43] An MCID of BPI in patients with XLH was not identified from the literature.

In Study CL303, change from baseline in BPI worst pain score was a key secondary efficacy end point, and changes from baseline in BPI pain severity score and BPI pain interference score were additional secondary efficacy end points.

Brief Fatigue Inventory

The BFI is a self-reported questionnaire to assess the severity of fatigue and the impact of fatigue on daily functioning. Two dimensions are measured in this nine-item instrument: fatigue (three items) and the interference of fatigue on daily life (six items pertaining to general activity, mood, walking ability, normal work, relations with others, and enjoyment of life). The items are measured on a 0 to 10 numeric rating scale. For the dimension of severity of fatigue, 0 represents "no fatigue" and 10 represents "fatigue as bad as you can imagine." For the dimension of interference from fatigue, 0 represents "does not interfere" and 10 represents "completely interferes." A score of 7 to 10 is considered severe fatigue.[44] A global fatigue score can be obtained by averaging all the items on the BFI.[45] BFI has been validated and used in patients with various conditions, including cancer, osteoarthritis, and rheumatoid arthritis.[12] The construct validity, concurrent validity, and discriminant validity of the BFI have been demonstrated in cancer patients. The reliability of the BFI was excellent (coefficient alphas were 0.95 to 0.96), based on one study including 305 adult patients with cancer.[44] An MCID for the BFI in patients with XLH was not identified in the literature.

Change from baseline in BFI worst fatigue score and in the BFI global fatigue score were additional secondary efficacy end points in Study CL303.

Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC is a self-administered questionnaire assessing pain, stiffness, and physical functioning in patients with hip and knee osteoarthritis. It is a valid, reliable, and responsive measure of outcome in knee osteoarthritis,[46-48] and has been widely used in other painful musculoskeletal disorders, such as lower back pain, rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia.[49] The WOMAC consists of 24 items divided into three subscales:[50]

- pain (five items): during walking, using stairs, in bed, sitting or lying, and standing upright
- stiffness (two items): after first waking and later in the day
- physical function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in or out of a car, shopping, putting on or taking off socks, rising from bed, lying in bed, getting in or out of a bath, sitting, getting on or off the toilet, heavy domestic duties, light domestic duties.

There are two scale formats for the WOMAC: a 10 cm Visual Analogue Scale (VAS) and a 5-point Likert scale. The two were found to be highly correlated and to yield similar precision for discriminating between treatments in patients with osteoarthritis.[51] The Likert version of the WOMAC was used in Study CL303. It is rated on an ordinal scale of 0 to 4, where 0 means the lowest level of symptoms or physical disability. Each subscale is summated to maximum scores of 20, 8, and 68, respectively, providing a maximum global score of 96 (the sum of the three subscales).[52] Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations. An MCID for improvement or worsening was not identified for the Likert format of WOMAC.

In Study CL303, changes from baseline to week 24 in the WOMAC stiffness score and in the WOMAC physical function score were key secondary efficacy end points.

Faces Pain Scale – Revised

The FPS is a self-reported measure for evaluating pain intensity in children.[53] It consists of a series of horizontal gender-neutral faces that depict a neutral facial expression of “no pain” on the left to “most pain possible” on the right. The FPS has seven faces scoring from 0 to 6, with higher scores indicating more severe pain. The revised version (FPS-R) has six faces scoring from 0 to 10. Patients are instructed to point to the face that shows how much they hurt. The FPS-R is reliable and validated for assessing pain intensity in children. An MCID has not been specified for the FPS-R.

Change from baseline in the FPS-R was a secondary end point in Study CL301. In Study CL301, only patients who were at least five years of age at the time of the screening visit completed this measure.

6-Minute Walk Test

The 6MWT is a supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.[54] A specific protocol outlining training, level of support provided to the patient, and standardization of distance available for the patient to walk (30 m) is provided by the American Thoracic Society.[54]

A systematic review of the literature on the 6MWT in the pediatric population across nine conditions, including those with musculoskeletal disorders, identified several issues associated with use of the test in this population.[55] MCID values reported in the systematic

review ranged from 36 m in patients with spina bifida to 68 m in obese patients. Other studies have found that the age, height, and weight of a child can have an impact on the distance travelled in six minutes. This may have an impact on 6MWT results obtained from trials of longer duration.[56] The reliability and validity of the 6MWT were evaluated in 24 patients with hypophosphatasia. The test-retest reliability was high for children, adolescents, and adults (Pearson's correlation coefficients ranged from 0.81 to 0.95). MCIDs for patients with hypophosphatasia were estimated using distribution-based methods (31 m for children and adults and 43 m for adolescents).[57]

Change from baseline in the 6MWT total distance and percentage of predicted normal was a secondary efficacy end point in Study CL201, a secondary end point in Study CL301, and an exploratory efficacy end point in Study CL303. In Study CL301, only patients who were at least five years of age at the time of the screening visit completed this measure.

PROMIS Scores for Pediatric Pain Interference, Fatigue, and Physical Function Mobility Scales

The PROMIS is a set of measures covering different domains of physical, mental, and social health.[58] It contains a bank of questions from which relevant items can be extracted and used to create a custom form. At present, PROMIS assesses 51 distinct health domains for adults and 18 distinct health domains for the pediatric population. The PROMIS relies on large collections of items (item banks) for each individual health domain. The output from a PROMIS score is a t score, which is a standardized score developed using a representative sample of the entire population. The t score has a mean of 50 (SD = 10) in that population. The t scores are generated for each domain based on the questions included for scoring. Higher scores represent more of what is measured — for example, more mobility, more pain, or more fatigue.[13] There is no information available regarding the MCID for PROMIS domains in various populations.

In Study CL301, the PROMIS pain interference, physical function mobility, and fatigue questionnaires were administered to patients aged greater than or equal to five years.[13] Changes from baseline in the PROMIS scores in pediatric pain interference, physical function mobility, and fatigue domains were other secondary end points.

Pediatric Orthopaedic Society of North America – Pediatric Outcomes Data Collection Instrument

The PODCI is a self-reported generic measure for children aged two years to 18 years with chronic health disorders, specifically any problems related to bone and muscle conditions.[59] It was designed to evaluate overall health, pain, and ability to participate in normal daily activities, as well as more vigorous activities typically associated with young people. It includes a pediatric version to be completed by a parent and an adolescent version that can be completed by the parent, child, or both. It contains five scales that provide a broad view of the physical, mental, and psychosocial status of the child or adolescent patient. The questionnaire yields a global function score, a happiness score, and four functional assessment scores (upper extremity functioning, transfers and basic mobility, sports and physical functioning, and comfort and pain). The global function score is an average of the four functional scores. Standardized scores range from 0 to 100, with 0 representing the poorest outcome or worst health, and 100 representing the best possible outcome or best health. To make the standard scores comparative across various scales, data from the general US population were transformed for each scale so that the normative score for each scale has a mean of 50 and an SD of 10. Thus, a patient scoring above 50 on a

particular scale is above the general population's average, while a patient scoring below 50 on a scale is below the general healthy population's average. In the PODCI, higher scores represent less disability and better functioning.

Responsiveness in patients with XLH was inconclusive. An MCID for the PODCI was not identified for patients with XLH.

Change from baseline in the POSNA-PODCI sports and physical functioning scale and the PODCI pain and comfort scale were secondary end points in Study CL201.

The Bruininks-Oseretsky Test of Motor Proficiency – Second Edition

The Bruininks-Oseretsky Test of Motor Proficiency – Second Edition (BOT-2) is intended for use by practitioners and researchers as a discriminative and evaluative measure to characterize motor performance, specifically in the areas of fine manual control, manual coordination, body coordination, and strength and agility.[60] It is an instrument that measures fine and gross motor skills in individuals aged four years to 21 years. In Study CL201, the BOT-2 used a composite score from two subtests: running speed and agility, and strength.[10] The maximum score for the running speed and agility subtest is 52. The maximum score for the strength subtest is 42. The point scores for all of the items in each subtest are summed to get the total point scores for the BOT-2. The increase of the total point scores represents an improvement. An MCID for the BOT-2 was not identified.

The change from baseline in the BOT-2 subtests for running speed and agility and strength were exploratory efficacy end points in the CL201 study.

Short Form (10) for Children Health Survey

The SF-10 is a parent-completed questionnaire intended to assess the health status of children aged five years to 18 years.[61] It is part of the Quality Metric Pediatric Health Surveys and was adapted from the Child Health Questionnaire. The SF-10 contains 10 Likert-type scale items (graded using 4- and 5-point responses) that use a four-week recall period and yield physical and psychosocial health summary baseline scores for the following physical and psychosocial concepts: physical functioning, role/social physical, general health perceptions, bodily pain, role/social emotional-behavioural, self-esteem, mental health, and general behaviour. Responses were used to generate two component summary scores: PHS and PSS. Scale scores are standardized to a mean of 50 and an SD of 10 in the combined US general population. Higher scores are associated with better quality of life. There is evidence supporting the reliability, validity, and discriminating ability of the SF-10 in the general US population of children with or without a chronic condition or disability. The summary measures were internally consistent across groups with and without disability: for physical summary scores, the alpha levels were 0.78 and 0.76, respectively; for psychosocial summary scores, the alpha levels were 0.80 and 0.72, respectively. No data regarding its responsiveness are available.[61,62] An MCID for the SF-10 was not specified in children with XLH.

Changes from baseline in the SF-10 for Children Health Survey PHS and PSS were exploratory efficacy end points in the CL301 and CL201 studies. In the CL301 study, only patients who were at least five years of age at the time of the screening visit completed this questionnaire.

Safety

An AE was defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it was considered drug-related. Therefore, an AE can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), a symptom, or a disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) products.

An SAE was defined as an AE or suspected adverse reaction that at any dose, in the view of either the investigator or the sponsor, results in death, a life-threatening AE, inpatient hospitalization, prolongation of an existing hospitalization, persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions), or a congenital anomaly or birth defect.

Statistical Analysis

Study CL301

The sample size in the CL301 study was calculated using a two-sample t-test with a two-sided alpha level of 0.05. The determination of sample size was based on the assumption that the mean RGI-C global score would be +1.80 in the burosumab group and +1.40 in the active-control group (oral phosphate and active vitamin D), with a common SD of 0.50. Given these assumptions, a total sample size of 60 (30 per group) would provide approximately 80% power to detect such a difference in the mean RGI-C global score at week 40 between treatment groups. A 10% dropout rate was incorporated in the sample size calculation.

In Study CL301, the primary efficacy end point was the change in rickets at week 40 as assessed by the RGI-C global score. For the growth-related end points, RGI-C long leg score, and change from baseline in standing height or recumbent length z score, the primary assessment time was at week 64. For other secondary end points, the primary assessment time was week 40. No adjustments for multiplicity were performed for the secondary end points.

In Study CL301, an analysis of covariance (ANCOVA) model with treatment group and baseline age stratification factor as independent variables and baseline RSS total score as a continuous covariate was used for the analysis of the primary efficacy outcome (the RGI-C global score).

In the base-case analysis, no imputation of missing data was made. Sensitivity analyses to assess the robustness of the primary analysis result to missing data were conducted on RSS and RGI-C end points using the last observation carried forward and multiple imputation methods.

For the RGI-C knee, wrist, and lower limb deformity scores, an ANCOVA model similar to that used for the primary end point was applied, with baseline RSS wrist score used in the RGI-C wrist score modelling and baseline RSS knee score used in the RGI-C knee score and lower limb deformity score modelling.

The proportion of RGI-C responders (patients with a mean RGI-C global score ≥ +2.0) was summarized for each treatment group. A logistic regression model was applied, with treatment group and baseline age stratification factor as independent variables and baseline RSS total score as a continuous covariate.

The change from baseline in RSS (total, knee, and wrist) scores over time was analyzed using the same method as that used for the RGI-C score.

The changes in serum phosphorus from baseline were analyzed using an ANCOVA model. Treatment group, baseline age, and RSS total score stratification factors (RSS total score ≤ 2.5 versus > 2.5) were included as independent variables; baseline serum phosphorus was included as a continuous covariate.

An ANCOVA model was applied to the change in growth velocity z score from baseline to week 40 and week 64 to assess the difference between treatment groups. The treatment-group and baseline RSS total score stratification factors (RSS total score ≤ 2.5 versus > 2.5) were independent variables; baseline z score and age were included as continuous covariates.

For repeated measures, the generalized estimating equation (GEE) approach was used to assess the change over time for the outcomes listed here. The GEE model included treatment group, study visit, interaction between treatment group and study visit, and baseline age stratification factor as independent variables, with baseline RSS total score as a continuous covariate. The following outcomes were analyzed using the GEE method:

- change from baseline in RGI-C global score at week 64
- RGI-C long leg score at week 40 and week 64
- change from baseline in RSS total score at week 64
- change from baseline in ALP at week 40 and week 64
- RGI-C knee and wrist scores at week 64
- change from baseline in RSS knee and wrist scores at week 64
- change from baseline in PROMIS pain interference, fatigue, and physical function mobility scores
- change from baseline in FPS-R score
- change from baseline in 6MWT total distance and percentage of predicted normal
- change from baseline in pharmacodynamic parameters at week 40 and week 64.

Subgroup analysis by RSS total score ≤ 2.5 versus > 2.5) and age (< five years versus ≥ five years old) were conducted for specified efficacy end points, including rickets, growth, and serum phosphorus.

Study CL201

In the CL201 study, a sample size of 10 patients per cohort was planned to provide 90% statistical power to detect a serum phosphorus increase from baseline of at least 0.26 mmol/L, assuming an SD of 0.23 mmol/L or smaller, at the two-sided level of significance of 0.05.

The primary efficacy end point was the change from baseline in severity of rickets as measured by RSS total score. Change from baseline in severity of rickets as measured by RSS knee and wrist scores, change from baseline in the radiographic appearance of rickets and bowing as measured by RGI-C global, knee, wrist and long leg scores, growth (standing height), walking ability (using the 6MWT), and the functional disability and pain assessment (using POSNA-PODCI) were secondary end points. Statistical tests were two-sided at the alpha significance level of 0.05, and 95% CIs were used. All P values were

presented as nominal P values. No adjustments for multiplicity were performed. No imputation of missing data was performed.

A GEE model was used, with all RSS change from baseline data as independent variables and baseline RSS total score as covariate. Regimen group, study visit, and interaction between regimen and study visit as categorical independent variables were used for the analysis of the primary efficacy outcome (RSS total score). A supportive analysis was also performed using a one-sample, paired t-test (null hypothesis of no change from baseline of RSS total score); if the normality assumption was not satisfied, the sign test was to be used.

For RSS knee and wrist scores, a GEE model similar to that used for the primary end point was applied.

A GEE model was used for the analysis of RGI-C, with all RGI-C data (global, knee, wrist, and long leg) scored separately, as independent variables. Covariates were baseline RSS total score for RGI-C global score, baseline RSS wrist score for RGI-C wrist score, and baseline RSS knee score for RGI-C knee and lower limb deformity scores. Categorical independent variables were regimen group, study visit, and interaction between regimen and study visit. RGI-C evaluations of lower extremity deformities were analyzed in the same manner as the RGI-C evaluations of rickets.

Change from baseline in standing height was assessed using a GEE model, with standing height z score at selected study visits as independent variable; baseline height, age, and gender as candidate covariates; and regimen group, study visit, and interaction between regimen and study visit as categorical independent variables.

Changes from baseline in total distance walked and in results for percentage of predicted 6MWT were assessed using the GEE approach with the baseline measure included in the model as covariate. The percentage of predicted values was calculated using published normative data based on age, gender, and height.[63]

Changes from baseline in the standardized score and normative score of the POSNA-PODCI over time were assessed using the GEE approach.

For efficacy analyses, subgroup analysis by baseline rickets severity (RSS total score < 1.5 versus ≥ 1.5) were conducted. For analysis of 6MWT results, subgroups were defined based on the baseline percentage of predicted 6MWT (< 80% [abnormal] or ≥ 80% [normal]). For analysis of POSNA-PODCI questionnaire results, subgroups were defined based on the baseline global functioning scale (< 40 or ≥ 40).

Study CL205

Study CL205 planned to enrol approximately 10 children aged one year to four years with XLH. A sample size of 10 patients was considered appropriate to evaluate the burosumab dose and the pharmacodynamic relationship to confirm if the profile was similar in patients aged one year to four years to that observed in older children (aged five years to 12 years) in the CL201 study.

Changes from baseline to post-baseline time points in pharmacodynamic and efficacy parameters were tested for statistical significance. Statistical tests were two-sided at the alpha significance level of 0.05; 95% CIs were used. All P values were presented as nominal P values. No adjustment for multiplicity was performed. No imputation of missing data was conducted.

An ANCOVA model was applied to each RGI-C score (wrist, knee, global, and lower limb deformity) and to change from baseline in each RSS score (wrist, knee, and total). The ANCOVA model for RSS scores included the change from baseline in RSS score as the dependent variable and age and the RSS score at baseline as covariates. The ANCOVA model for RGI-C scores included the RGI-C score as the dependent variable and age and RSS at baseline as covariates. By-visit analyses using the GEE model were applied for all pharmacodynamic parameters; the GEE model included change from baseline as the dependent variable and time as the categorical variable, and adjusted for baseline measurement, with exchangeable covariance structure. By-visit analyses using the GEE model were was applied to recumbent length or standing height; the GEE model included the change from baseline as the dependent variable, visit and gender as factors, and age and recumbent length or standing height z score at baseline as covariates, with exchangeable covariance structure.

Study CL303

In Study CL303, a sample size of 60 per group (total sample size of 120) was planned to provide 95% statistical power to detect a 50% difference between the burosumab and placebo groups in the percentages of patients achieving mean serum phosphorus levels at the midpoint and end-of-dose intervals between baseline and week 24 at the two-sided significance level of 0.05. The determination of the sample size for this study was based on the assumption that the percentage of patients who achieved mean serum phosphorus levels in the normal range at the midpoint of the dose interval from baseline to week 24 would be 60% and 10% in the burosumab and placebo groups, respectively. With a total sample size of 120 patients, this study design also had greater than or equal to 80% power to detect a mean difference of 1.0 in change from baseline between the burosumab and placebo groups in BPI worst pain, assuming a mean change from baseline of 2.0 in the burosumab group and of 1.0 in the placebo group, a common SD of 1.8, and a 10% dropout rate.

The primary efficacy end point was analyzed using the Cochran-Mantel-Haenszel test to compare the percentages of patients in the burosumab and placebo groups who achieved a serum phosphorus level above the LLN (0.81 mmol/L) at the midpoint of the dosing interval, as averaged across dose cycles between baseline and week 24, adjusting for the BPI average pain (> 6.0 or ≤ 6.0) and geographic region stratification factors used for randomization. The primary end point was tested at the two-sided alpha level of 0.05.

The three key secondary efficacy end points (change from baseline to week 24 in BPI worst pain, WOMAC stiffness, and WOMAC physical function scores) were tested between treatment groups. These end points were analyzed at a two-sided alpha level of 0.05 using GEE repeated measures analysis. The GEE model included treatment and BPI average pain randomization stratification factors (if applicable) and region, visit, and interaction of treatment by visit as fixed factors; it was adjusted for baseline measurement. The BPI average pain stratification factor was not included in the GEE model for the change from baseline in BPI worst pain because baseline BPI worst pain was highly correlated with the BPI average pain randomization stratification factor.

At week 24, analyses of additional secondary end points and exploratory end points used methods similar to those for the primary end point and key secondary end points whenever applicable.

In order to control the family-wise error rate at the 0.05 level, the following method was used for multiple testing with regard to the primary and key secondary efficacy end points

(change from baseline to week 24 in BPI worst pain, WOMAC stiffness, and WOMAC physical function scores). First, if the primary efficacy end point was statistically significant (i.e., the burosumab group was superior to the placebo group [P value < 0.05 by a two-sided test]), then the three key secondary end points were tested as a group at the 0.05 level. The Hochberg adjustment was applied for multiple testing for the three end points, ordering the nominal P values for the end points from largest to smallest to determine the significance level at which they were tested. The largest P value was tested at a significance level of 0.05; the second-largest P value was tested at a significance level of 0.025; and the smallest P value was tested at a significance level of 0.0167. No multiplicity adjustments were made for the remaining secondary efficacy end points.

No imputation of missing data was made.

Subgroup analyses by baseline BPI average pain (> 6.0 or ≤ 6.0) were performed for selected efficacy end points.

Analysis Populations

In Study CL301, the efficacy analyses were based on the full analysis set (FAS). The FAS included all randomized patients who received at least one dose of assigned medication and had at least one post-baseline assessment. Patients were analyzed according to the assigned treatment at randomization.

In Study CL201, the efficacy analyses were based on the intention-to-treat (ITT) set, which consisted of all patients who received at least one dose of study therapy and had at least one post-dose measurement.

In Study CL205, the efficacy analyses were based on the efficacy analysis set, which was similar in definition to that of the ITT set used in Study CL201.

In Study CL303, the efficacy analyses were based on the primary analysis set (PAS), which included all randomized patients who received at least one dose of the study drug during the placebo-controlled treatment period. Patients were analyzed according to the randomized treatment group regardless of the actual treatment received.

In studies CL301, CL201, and CL205, the pharmacodynamic analysis set consisted of all patients who received at least one dose of therapy and had evaluable serum data.

In all of the included studies, the safety analysis set (SAS) consisted of all randomized patients who received at least one dose of the study drug. Patients were analyzed based on the actual treatment received.

Results

Patient Disposition

Patient disposition is summarized in Table 11.

In Study CL301, a total of 122 patients were screened. Among them, a total of 61 patients failed to meet one or more eligibility criteria. The most common reasons for screen failure were RSS total score of less than 2 (55 patients), serum phosphorus concentration greater than or equal to 0.97 mmol/L (13 patients), and serum calcium concentration outside of the reference range (six patients). (Patients could have more than one reason for screen failure.) A total of 61 pediatric patients were enrolled in the study and randomized 1:1 to the burosumab (29 patients) and active-control (32 patients) groups. All patients completed at least 64 weeks in the study. None discontinued treatment or the study.

In Study CL201, a total of 79 patients were screened. Among them, 27 were not enrolled because they did not meet one or more entry criteria. Eighteen patients did not have radiographic evidence of active bone disease; four were at a Tanner stage greater than 2; three did not have biochemical findings associated with XLH (including two who did not have radiographic evidence of active bone disease); and one did not have confirmation of XLH supported by PHEX mutation or elevated serum FGF23. In addition, three patients had a nephrocalcinosis grade greater than or equal to 3 by renal ultrasound. A total of 52 pediatric patients were enrolled in the study and randomized 1:1 to every-two-weeks regimens (26 patients) or every-four-weeks regimens (26 patients). All 52 patients completed at least 64 weeks in the study. None discontinued the study.

In Study CL205, 13 pediatric patients were enrolled. All completed week 40; none discontinued treatment or the study. One patient screened for the study was not enrolled because they did not meet the entry criteria for biochemical findings associated with XLH (i.e., serum phosphorus and creatinine levels).

In Study CL303, a total of 163 patients were screened. Among them, 134 patients were enrolled and randomized 1:1 to burosumab (68 patients) or placebo (66 patients). The most common reason for being screened out (reported for 10 patients) was failure to meet the inclusion criterion requiring presence of skeletal pain attributed to XLH or osteomalacia, defined by a score of greater than or equal to 4 in BPI worst pain, at the first screening visit. The next most common reason (applicable to five patients) was meeting the exclusion criterion of having serum intact PTH greater than or equal to 2.5 times the ULN at the first screening visit. All 134 patients (100.0%) who enrolled in the study received at least one dose of the study drug and were included in the PAS and SAS. All but one patient (who was in the burosumab group) completed the 24-week, placebo-controlled treatment period. The patient who discontinued withdrew consent for participation in the study after approximately six months of treatment (with the last dose of burosumab administered approximately one month before study withdrawal) and did not complete the week 24 visit assessment.

Table 11: Patient Disposition

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks	Phosphate and active vitamin D	Burosumab every two weeks	Burosumab every two weeks	Burosumab every four weeks	Placebo
Screened, N	122		79	14	163	
Randomized, N	29	32	26	13	68	66
Discontinued, N (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	0 (0)
Reason for discontinuation, N (%)						
Patient withdrew consent	0	0	0	0	1 (1.5)	0 (0)
FAS, N (%)	29 (100)	32 (100)	NA	NA	68 (100)	66 (100)
ITT, N (%)	NR	NR	26 (100)	13 (100)	NR	NR
Primary analysis set, N (%)	NA	NA	NA	NA	68 (100)	66 (100)
PP, N	NR	NR	NR	NR	NR	NR
PD analysis set, N (%)	29 (100)	32 (100)	26 (100)	13 (100)	NR	NR
Safety, N (%)	29 (100)	32 (100)	26 (100)	13 (100)	68 (100)	66 (100)

FAS = full analysis set; ITT = intention to treat; NA = not applicable; NR = not reported; PD = pharmacodynamic; PP = per protocol.

Source: Clinical Study Reports for studies CL301, CL201, CL205, and CL303.[10-13]

Exposure to Study Treatments

In Study CL301, the mean duration of exposure to burosumab in the treatment period was 15.13 (SD = 0.17) months; the duration of exposure ranged from 14.7 months to 15.3 months. During the 64-week treatment period, all patients in the burosumab group received all planned doses of burosumab, except for three out of 29 (10%) patients, who missed one dose each. Most patients in the burosumab group (21 out of 29 [72%]) received the assigned dose of 0.8 mg/kg; eight patients (28%) had dose increases of burosumab to 1.2 mg/kg based on protocol-defined criteria. All eight continued at the 1.2 mg/kg dose through to week 64.

The mean duration of exposure to oral phosphate/active vitamin D in the active-control group during the study was 15.11 (SD = 0.22) months; duration of exposure ranged from 14.7 months to 15.5 months. The mean oral phosphate dose in the conventional therapy arm was within the recommended range (20 mg/kg/day to 60 mg/kg/day divided into three to five doses per day) (Table 12).[3] Mean daily doses of active vitamin D were generally in the recommended range (i.e., alfacalcidol 40 ng/kg/day to 60 ng/kg/day or calcitriol 20 ng/kg/day to 30 ng/kg/day divided into two or three doses per day).[3] However, it seems that some patients were not receiving the recommended dose of vitamin D. (The number of patients who were not receiving the recommended dose of vitamin D was not reported.)

Table 12: Daily Doses of Oral Phosphate and Active Vitamin D in the Active-Control Group in Study CL301

	Oral phosphate, mg/kg (N = 32)		Oral calcitriol ng/kg (N = 22)		Oral alfacalcidol, ng/kg (N = 9)[a]	
Visit	**Median (Q1, Q3)**	**Mean (SD) (range)**	**Median (Q1, Q3)**	**Mean (SD) (range)**	**Median (Q1, Q3)**	**Mean (SD) (range)**
Baseline	32.0 (25.6 to 52.9)	36.2 (16.0) (10.4 to 73.6)	21.2 (15.9 to 26.7)	21.6 (7.4) (6.8 to 34.6)	62.3 (34.5 to 104.7)	78.1 (66.4) (17.0 to 224.1)
Week 40	35.3 (28.4 to 50.5)	41.0 (20.7) (18.1 to 109.5)	22.3 (17.5 to 32.7)	26.4 (13.3) (6.8 to 63.5)	79.7 (40.2 to 104.7)	87.1 (61.4) (27.6 to 224.1)
Week 64	39.3 (28.7 to 52.9)	45.8 (27.7) (18.1 to 166.2)	26.4 (17.3 to 34.2)	27.2 (13.4) (6.8 to 63.5)	79.8 (40.2 to 104.7)	86.5 (59.6) (27.6 to 217.4)

Q1 = first quartile; Q3 = third quartile.

[a] One patient was not included in the oral alfacalcidol results because this patient received eldecalcitol (19.5 ng/kg/day) at baseline and switched to alfacalcidol at week 32 (11.2 ng/kg/day, with no dose adjustments thereafter).

Source: Clinical Study Report for Study CL301.[13]

In Study CL201, for the every-two-weeks treatment group, the mean burosumab dose per administration increased from 0.24 mg/kg at baseline (range: 0.1 mg/kg to 0.3 mg/kg) to 0.73 mg/kg at week 16 (range: 0.3 mg/kg to 1.5 mg/kg), 0.98 mg/kg at week 40 (range: 0.4 mg/kg to 2.0 mg/kg), and 1.05 mg/kg at week 64 (range: 0.4 mg/kg to 2.0 mg/kg) (Table 13).

Table 13: Weight-Based and Total Burosumab Doses at Four-Week Intervals (ITT Analysis Set) in Study CL201

Visit	Mean (SD) per administration (N = 52)
	Burosumab every two weeks mean (SD) [range]
Baseline	0.24 (0.081) [0.1 to 0.3]
Week 4	0.40 (0.143) [0.2 to 0.6]
Week 8	0.53 (0.216) [0.2 to 0.9]
Week 12	0.63 (0.274) [0.2 to 1.2]
Week 16	0.73 (0.338) [0.3 to 1.5]
Week 20	0.77 (0.332) [0.3 to 1.5]
Week 24	0.83 (0.342) [0.4 to 1.5]
Week 28	0.84 (0.366) [0.4 to 1.8]
Week 32	0.90 (0.408) [0.4 to 2.0]
Week 36	0.90 (0.408) [0.4 to 2.0]
Week 40	0.98 (0.447) [0.4 to 2.0]
Week 44	0.99 (0.460) [0.4 to2.0]
Week 48	0.99 (0.458) [0.4 to 2.0]
Week 52	1.02 (0.468) [0.4 to 2.0]
Week 56	1.04 (0.484) [0.4 to 2.0]
Week 60	1.04 (0.488) [0.4 to 2.0]
Week 64	1.05 (0.486) [0.4 to 2.0]

ITT = intention to treat; SD = standard deviation.

Source: Clinical Study Report for Study CL201.[10]

In Study CL205, all patients received all planned doses of burosumab at a prescribed dose of 0.8 mg/kg every two weeks through week 20, and 10 patients continued to receive burosumab at 0.8 mg/kg every two weeks through week 40. Three patients had dose increases to 1.2 mg/kg every two weeks based on the protocol-specified dose-adjustment criteria (at week 22 for two patients and at week 34 for one patient); the burosumab dose continued at the higher dose through to week 40. The mean total dose per administration through week 40 ranged from 10.2 mg to 13.0 mg.

Throughout Study CL303, patients received stable doses of the study drug, based on 1.0 mg/kg dosing. The protocol included criteria for treatment assignment unblinding and dose adjustments due to elevated serum phosphorus levels. Most patients did not require dose adjustments. During the placebo-controlled treatment period, five patients (7.4%) in the burosumab group and none in the placebo group had treatment unblinded per-protocol. During the placebo-controlled treatment period, two patients in the placebo group each missed one dose of the study drug.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported here. See Appendix 3 for detailed efficacy data.

Rickets Severity Score

Change from baseline in severity of rickets as measured by RSS total score was a primary outcome in the CL201 study and a key secondary outcome in the CL301 and CL205 studies. Change from baseline in severity of rickets as measured by RSS knee and wrist scores were secondary outcomes in the CL301, CL201, and CL205 studies. The percentage of patients with an RSS total score reduction from baseline of at least 1.0 among those with a baseline RSS total score of at least 1.0 (“RSS responders”) — and the percentage of patients who healed completely among those with a baseline RSS total score greater than 0 (“complete RSS responders”) — were also reported.

Study CL301

For RSS total score, the difference between the burosumab group and the active-control group in change from baseline at week 40 was −1.34 (95% CI, −1.74 to −0.94; P < 0.0001) in favour of burosumab; at week 64, it was −1.21 (95% CI, −1.59 to −0.83; P < 0.0001) in favour of burosumab (Table 14).

Week 40 RSS knee and total scores were missing for one patient. A sensitivity analysis was performed to assess the robustness of the primary analysis result to missing data. The baseline knee score was used to impute the week 40 knee score and to derive the week 40 total score. The results of this analysis using last observation carried forward were very similar to those of the primary analysis.

Differences in RSS total score between the treatment groups were analyzed in subgroups of baseline rickets severity (RSS total score ≤ 2.5 versus > 2.5) and age (< five years versus ≥ five years old). Efficacy in the subgroups was similar to that of the overall study population (Table 43).

All patients (29 out of 29 [100%]) in the burosumab treatment group achieved reduction from baseline of at least 1 point in RSS total score at week 64 versus half of the patients in the placebo group (16 out of 32). Four patients (13.8%) in the burosumab treatment group

achieved an RSS total score of 0 (healed completely) at week 64 versus none in the placebo group (Table 14).

For RSS knee score, the difference between the burosumab group and the active-control group in change from baseline at week 40 was −0.69 (95% CI, −0.91 to −0.46; P < 0.0001) in favour of burosumab; at week 64, it was −0.58 (95% CI, −0.80 to −0. 36; P < 0.0001) in favour of burosumab (Table 42).

For RSS wrist score, the difference between the burosumab group and the active-control group in change from baseline at week 40 was −0.69 (95% CI, −0.97 to −0.41; P < 0.0001) in favour of burosumab; at week 64, it was −0.65 (95% CI, −0.90 to −0. 39; P < 0.0001) in favour of burosumab (Table 42).

Study CL201

In the group receiving burosumab every two weeks, the RSS total score at week 40 was reduced by −1.06 (95% CI, −1.28 to −0.85; P < 0.0001); at week 64, it was reduced by −1.00 (95% CI, −1.22 to −0.79; P < 0.0001) (Table 14).

Of the 20 patients who had an RSS total score of greater than or equal to 1.0 at baseline, 14 patients (70%) achieved a reduction from baseline at least 1 point in RSS total score at week 64. Of the 25 patients who had a baseline RSS total score higher than 0, six patients (24%) achieved an RSS total score of 0 (healed completely) at week 64 (Table 14).

In the group receiving burosumab every two weeks, the RSS knee score at week 40 was reduced by −0.63 (95% CI, −0.82 to −0.43; P < 0.0001); at week 64, it was reduced by −0.70 (95% CI, −0.87 to −0.53; P < 0.0001) (Table 44).

In the group receiving burosumab every two weeks, the RSS wrist score at week 40 was reduced by −0.44 (95% CI, −0.53 to −0.35; P < 0.0001); at week 64, it was reduced by −0.30 (95% CI, −0.42 to −0.19; P < 0.0001) (Table 44).

Study CL205

RSS total score at week 40 was reduced by −1.73 (95% CI, −2.03 to −1.44; P < 0.0001) in the group receiving burosumab every two weeks (Table 14).

RSS knee score at week 40 was reduced by −0.96 (95% CI, −1.09 to −0.84; P < 0.0001) in the group receiving burosumab every two weeks (Table 44).

RSS wrist score at week 40 was reduced by −0.77 (95% CI, −0.99 to −0.54; P < 0.0001) in the group receiving burosumab every two weeks (Table 44).

Radiographic Global Impression of Change

Change from baseline in the radiographic appearance of rickets as measured by RGI-C global score was the primary outcome in Study CL301 and a key secondary outcome in studies CL201 and CL205. Change in lower extremity skeletal abnormalities as assessed by the RGI-C long leg score was a secondary outcome in studies CL301, CL201, and CL205. Change in rickets as assessed by RGI-C wrist score and knee score was a secondary outcome in studies CL301, CL201, and CL205. The proportion of patients with a mean RGI-C global score greater than or equal to +2.0 (substantial healing) was another efficacy end point in Study CL301.

Study CL301

For RGI-C global scores, the difference between the burosumab group and the active-control group in change from baseline at week 40 was 1.14 (95% CI, 0.83 to 1.45; P < 0.0001) in favour of burosumab; and at week 64, it was 1.02 (95% CI, 0.72 to 1.33; P < 0.0001) in favour of burosumab (Table 14).

Differences in RGI-C global scores between the treatment groups were analyzed in subgroups of baseline rickets severity (RSS total score ≤ 2.5 versus > 2.5) and age (< five years versus ≥ five years old). Efficacy in the subgroups was similar to that of the overall study population (Figure 2 and Figure 3).

Substantial healing of rickets, as assessed by RGI-C, was defined as an RGI-C global score of greater than or equal to +2.0 (i.e., substantial healing indicating improvement in the radiographic abnormalities; does not imply that complete healing) and was observed at week 40 in 72% and 6% of patients in the burosumab and active-control groups, respectively (odds ratio = 39.1; 95% CI, 7.2 to 211.7; P < 0.0001). At week 64, 86% and 19% of patients in the burosumab and active-control group, respectively, achieved substantial healing of rickets (odds ratio = 34.1; 95% CI, 5.6 to 206.3; P = 0.0002) (Table 14).

In the burosumab group, all patients (100%) had RGI-C global scores greater than or equal to +1.0 (i.e., at least minimal healing and including substantial healing) by week 40. In the active-control group, 17 out of 32 patients (53%) had RGI-C global scores greater than or equal to +1.0; 11 out of 32 patients (34%) had RGI-C global scores greater than 0 to 1; and 4 out of 32 patients (13%) had RGI-C global scores of less than 0 to –1 (i.e., minimal worsening of rickets) (Table 45).

For RGI-C knee scores, the difference between the burosumab group and the active-control group in change from baseline at week 40 was 1.12 (95% CI, 0.84 to 1.41; P < 0.0001) in favour of burosumab; at week 64, it was 1.01 (95% CI, 0.71 to 1.30; P < 0.0001) in favour of burosumab (Table 45).

For RGI-C wrist scores, the difference between the burosumab group and the active-control group in change from baseline at week 40 was 1.31 (95% CI, 0.89 to 1.74; P < 0.0001) in favour of burosumab; at week 64, it was 1.15 (95% CI, 0.78 to 1.51; P < 0.0001) in favour of burosumab (Table 45).

For RGI-C lower limb deformity scores, the difference between the burosumab group and the active-control group in change from baseline at week 40 was 0.41 (95% CI, 0.07 to 0.75; P = 0.0204), in favour of burosumab; at week 64, it was 0.97 (95% CI, 0.57 to 1.37; P < 0.0001) in favour of burosumab (Table 45).

RGI-C lower limb deformity scores greater than or equal to +1.0 (i.e., at least minimal improvement) were observed for two out of 29 patients (69%) in the burosumab group and for seven out of 32 patients (22%) in the active-control group at week 64. RGI-C lower limb deformity scores of less than 0 (i.e., worsening abnormalities) were observed in three patients (10%) in the burosumab group at week 40. However, two of these three patients had scores of greater than 0 at week 64. RGI-C lower limb deformity scores of less than 0 were observed in seven out of 32 patients (22%) in the active-control group at week 40. Among these seven patients, five achieved a lower limb score of greater than or equal to 0

at week 64, while two patients maintained scores of less than 0 at week 64; additionally, two new patients had scores of less than 0 at week 64.

Study CL201

In the group receiving burosumab every two weeks, RGI-C global scores at week 40 were improved by 1.66 (95% CI, 1.48 to 1.84; P < 0.0001). At week 64, they were improved by 1.56 (95% CI, 1.34 to 1.78; P < 0.0001) (Table 14).

In the group receiving burosumab every two weeks, healing of rickets (defined as global scores ≥ +1.0) was observed in 88.5% of patients at week 40 and in 80.8% of patients at week 64 (Table 46). In the subgroup of patients whose baseline RSS total score was greater than or equal to 1.5, healing of rickets was observed in all patients (100%) at week 40 and at week 64. In the subgroup of patients whose baseline RSS total score was less than 1.5, healing of rickets was observed in 66.7% of patients at week 40 and in 44.4% at week 64 (Table 46).

In the group receiving burosumab every two weeks, substantial healing of rickets (defined as global scores ≥ +2.0) was observed in 69.2% of patients at week 40 and in 57.7% of patients at week 64 (Table 14). In the subgroup of patients whose baseline RSS total score was greater than or equal to 1.5, healing of rickets was observed in all patients (94.1%) at week 40 and in 82.4% of patients at week 64. In the subgroup of patients whose baseline RSS total score was less than 1.5, healing of rickets was observed in 22.2% of patients at week 40 and in 11.1% at week 64 (Table 46).

In the group receiving burosumab every two weeks, RGI-C knee scores at week 40 were improved by 1.60 (95% CI, 1.39 to 1.80; P < 0.0001); at week 64, they were improved by 1.57 (95% CI, 1.37 to 1.77; P < 0.0001) (Table 46).

In the group receiving burosumab every two weeks, RGI-C wrist scores at week 40 were improved by 1.63 (95% CI, 1.35 to 1.92; P < 0.0001); at week 64, they were improved by 1.65 (95% CI, 1.35 to 1.95; P < 0.0001) (Table 46).

Study CL205

RGI-C global scores improved by 2.33 at week 40 (95% CI, 2.16 to 2.51; P < 0.0001) in the group receiving burosumab every two weeks (Table 14).

RSS knee scores improved by 2.21 at week 40 (95% CI, 1.86 to 2.55; P < 0.0001) in the group receiving burosumab every two weeks (Table 46).

RSS wrist scores improved by 2.26 at week 40 (95% CI, 2.01 to 2.50; P < 0.0001) in the group receiving burosumab every two weeks (Table 46).

Table 14: Summary of Rickets Severity Score and Radiographic Global Impression of Change in Studies CL301, CL201, and CL205

	Study CL301		Study CL201	Study CL205
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
RSS total score				
Baseline – mean (SD)	3.17 (0.975)	3.19 (1.141)	1.92 (1.172)	2.92 (1.367)
Change from baseline to week 40 – LS mean (95% CI)	−2.04 (−2.33 to −1.75)	−0.71 (−0.98 to −0.43)	−1.06 (−1.28 to −0.85)	−1.73 (−2.03 to −1.44)
Treatment-group difference versus control (95% CI) at week 40	−1.34 (−1.74 to −0.94)		NA	NA
P value	< 0.0001[a]		< 0.0001	< 0.0001[a]
Change from baseline to week 64 – LS mean (95% CI)	−2.23 (−2.46 to −2.00)	−1.01 (−1.31 to −0.72)	−1.00 (−1.22 to −0.79)	NR
Treatment-group difference versus control (95% CI) at week 64	−1.21 (−1.59 to −0.83)		NA	NA
P value	< 0.0001[a]		< 0.0001	NR
Proportion of patients achieving reduction from baseline at least 1.0 at week 64, n/N (%)	29/29 (100)	16/32 (50)	14/20 (70.0)	NR
Proportion of patients healed completely at week 64, n/N (%)	4/29 (13.8)	0/32 (0)	6/25 (24.0)	NR
RGI-C global score				
Week 40 – LS mean (95% CI)	1.92 (1.70 to 2.14)	0.77 (0.56 to 0.99)	1.66 (1.48 to 1.84)	2.33 (2.16 to 2.51)
Treatment-group difference versus control (95% CI) at week 40	1.14 (0.83 to 1.45)		NA	NA
P value	< 0.0001		< 0.0001[a]	< 0.0001[a]
Week 64 – LS mean (95% CI)	2.06 (1.91 to 2.20)	1.03 (0.77 to 1.30)	1.56 (1.34 to 1.78)	NR
Treatment-group difference versus control (95% CI) at week 40	1.02 (0.72 to 1.33)		NA	NA
P value	< 0.0001[a]		< 0.0001[a]	NR
RGI-C responders (RGI-C global scores ≥ +2.0) at week 40	21 (72.4)	2 (6.3)	18/26 (69.2)	13 (100)
P value	< 0.0001[a]		NA	NA
RGI-C responders (RGI-C global scores ≥ +2.0) at week 64	25 (86.2)	6 (18.8)	15/26 (57.7)	NR
P value	0.0002[a]		NA	NA

CI = confidence interval; LS = least squares; NA = not applicable; NR = not reported; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SD = standard deviation.

[a] Outcome not adjusted for multiplicity.

Source: Clinical Study Reports for studies CL301, CL201, and CL205.[10,11,13]

Growth

Change from baseline in standing height, recumbent length z score, and growth velocity z score were the secondary end points in the CL301, CL201, and CL205 studies. The primary assessment time point for growth parameters in the CL301 and CL201 studies was at week 64, while it was at week 40 in the CL205 study.

Study CL301

The difference between the burosumab group and the active-control group in change from baseline in standing height or recumbent length z score at week 40 was 0.12 (95% CI, 0.01 to 0.24; P = 0.0408); at week 64, it was 0.14 (95% CI, 0.00 to 0.29; P = 0.0490) (Table 47).

The mean standing height or recumbent length percentile for age and gender in the burosumab group was 5.87 (SD = 9.976) at baseline, and the mean changes from baseline were 2.10 (SD = 4.060) at week 40 and 1.48 (SD = 6.364) at week 64. In the active-control group, the mean standing height or recumbent length percentile for age and gender was 5.74 (SD = 9.505) at baseline, and the mean changes were −0.30 (SD = 2.654) at week 40 and −0.68 (SD = 3.009) at week 64. No between-treatment group comparisons were conducted (Table 47).

In the burosumab group, mean growth velocity was 6.52 (SD = 4.035) cm/year at baseline, 7.03 (SD = 2.050) cm/year at week 40, and 6.65 (SD = 1.459) cm/year at week 64. The mean changes from baseline were 0.51 (SD = 2.754) cm/year at week 40 and 0.13 (SD = 3.226) cm/year at week 64. In the active-control group, mean growth velocity was 6.40 (SD = 2.386) cm/year at baseline, 6.27 (1.314) cm/year at week 40, and 5.94 (SD = 1.116) cm/year at week 64. The mean change from baseline was −0.12 (SD = 2.092) cm/year at week 40 and −0.46 (SD = 1.989) cm/year at week 64. No between-treatment group comparisons were conducted (Table 47).

The mean growth velocity z scores in the burosumab group were 0.53 (SD = 1.796) at week 40 and 0.34 (SD = 1.458) at week 64; the LS mean change was 1.76 (95% CI, 1.07 to 2.44) at week 40 and 1.53 (95% CI, 0.99 to 2.06) at week 64. In the active-control group, the mean growth velocity z scores were −0.37 (SD = 1.320) at week 40 and −0.75 (SD = 0.879) at week 64; the LS mean changes were 0.73 (95% CI, 0.05 to 1.42) at week 40 and 0.41 (95% CI, −0.13 to 0.94) at week 64. The difference between the treatment groups in change in z score at week 40 was 1.02 (95% CI, 0.06 to 1.99; P = 0. 0386); at week 64, it was 1.12 (95% CI, 0.37 to 1.88; P = 0. 0047) (Table 47).

Study CL201

In the CL201 study, burosumab treatment for 64 weeks increased growth velocity. The mean growth velocity increased from 5.45 (SD = 1.17) cm/year at baseline to 6.14 (SD = 1.466) cm/year at week 64, a 12% increase from baseline (Table 48).

The mean standing height z score increased from −1.72 (SD = 1.026) at baseline to −1.54 (SD = 1.127) at week 64, a change of 0.19 (95% CI, 0.09 to 0.29; P = 0.0002). Mean percentile standing heights were 11.13 (SD = 13.798) at baseline and 15.04 (SD = 17.443) at week 64 (Table 49).

In the subgroup of patients whose baseline RSS total score was ≥ 1.5, increases to week 64 were observed in both growth velocity (22%; P = 0.0076) and standing height z score (0.19; 95% CI, 0.05 to 0.32; P = 0.0063). In the subgroup of patients whose baseline RSS

total score was less than 1.5, change in growth velocity decreased by 3% at week 64, while standing height z score increased by 0.19 (95% CI, 0.07 to 0.31; P = 0.0017) (Table 48 and Table 49).

Study CL205

In the CL205 study, the mean standing height or recumbent length increased from 89.2 (SD = 7.6) cm at baseline to 93.4 (SD = 7.0) cm at week 40. All patients had increases in recumbent length or standing height from baseline to week 40; the median change from baseline was 4.10 cm, with a range of 0.1 cm to 9.4 cm (Table 50).

The mean standing height or recumbent length as a percentile for age and gender was 18.0% (SD = 25.3%) at baseline and 12.8% (SD = 18.9%) at week 40; the mean change was −5.3 (SD = 20.2) percentile points. The median standing height or recumbent length as a percentile for age and gender was 8.5% (range = 0.0% to 83.3%) at baseline and 5.4% (0.0% to 62.1%) at week 40; the median change was −0.3 (range = −70.4 to 9.82) percentile points (Table 50).

The mean standing height or recumbent length z score was −1.4 (SD = 1.19) at baseline and −1.7 (SD = 1.12) at week 40, a change of −0.3 (SD = 0.66). The median standing height or recumbent length z score was −1.4 (range = −3.66 to 0.97) at baseline and −1.6 (range = −4.03 to 0.31) at week 40, a median change of −0.2 (range = −2.10 to 0.29). The change from baseline in z score was –0.20 (95% CI, −0.46 to 0.06; P = 0.1396) (Table 50).

Serum Phosphorus

Change from baseline in serum phosphorus was the primary efficacy end point in the CL205 study and a secondary end point in the CL301 and CL201 studies. The proportion of patients achieving the normal range of serum phosphorus (1.03 mmol/L to 1.97 mmol/L) was also reported in studies CL301, CL201, and CL205. In Study CL303, the primary end point was the proportion of patients achieving mean serum phosphorus levels above the LLN (0.81 mmol/L) at the midpoint of the dose interval (i.e., weeks 2, 6, 10, 14, 18, and 22), as averaged across dose cycles between baseline and week 24.

Study CL301

In the CL301 study, mean fasting serum phosphorus concentrations increased in the burosumab group from 0.78 (SD = 0.077) mmol/L at baseline to 1.09 (SD = 0.120) mmol/L at week 40 and to 1.08 (SD = 0.117) mmol/L at week 64. Mean serum phosphorus concentrations in the active-control group increased from 0.74 (SD = 0.082) mmol/L at baseline to 0.82 (SD = 0.093) mmol/L at week 40 and to 0.83 (SD = 0.096) mmol/L at week 64. The difference in serum phosphorus between the burosumab group and the active-control group in change from baseline at week 40 was 0.25 mmol/L (95% CI, 0.20 to 0.30; P < 0.0001) in favour of burosumab; at week 64, it was 0.24 mmol/L (95% CI, 0.19 to 0.29; P < 0.0001) in favour of burosumab (Table 51).

Differences in serum phosphorus between the treatment groups were analyzed in subgroups of baseline rickets severity (RSS total score ≤ 2.5 versus > 2.5) and age (< five years versus ≥ five years old). Efficacy in the subgroups was similar to that of the overall study population (Table 52).

Of the 29 patients randomized to the burosumab treatment group, 17 patients (58.6%) and 19 patients (65.5%) had serum phosphorus concentrations within the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40 and week 64, respectively. Of the 32 patients

randomized to the active-control group (oral phosphate and active vitamin D therapy), only one patient (3.1%) had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40 and week 64 (Table 15).

Study CL201

In Study CL201, mean serum phosphorus levels increased in the burosumab-every-two-weeks group, from 0.77 (SD = 0.131) mmol/L at baseline to 1.07 (SD = 0.128) mmol/L at week 40 and 1.08 (SD = 0.144) mmol/L at week 64. At week 40, 17 out of 26 patients (SD = 65.4%) had serum phosphorus levels within the normal range (1.03 mmol/L to 1.97 mmol/L), as did 16 out of 24 patients (SD = 66.7%) at week 64 (Table 15 and Table 53).

Study CL205

In Study CL205, mean serum phosphorus levels increased in the burosumab-every-two-weeks group from 0.81 (SD = 0.092) mmol/L at baseline to 1.12 (SD = 0.158) mmol/L at week 40. Change from baseline to week 40 was 0.3 mmol/L (95% CI, 0.24 to 0.39; P < 0.0001). At week 40, 10 patients (SD = 76.9%) had serum phosphorus levels within the normal range (1.03 mmol/L to 1.97 mmol/L) (Table 15 and Table 53).

Study CL303

At baseline, the mean serum phosphorus concentration was below the LLN (SD = 0.81 mmol/L) in both treatment groups, at 0.66 (SD = 0.098) mmol/L in the burosumab group and 0.62 (SD = 0.102) mmol/L in the placebo group.

The primary end point analysis in Study CL303 demonstrated a statistically significant effect of burosumab relative to placebo in increasing serum phosphorus concentrations from baseline to week 24, with a total of 94.1% of patients in the burosumab group achieving a mean serum phosphorus concentration above the LLN across the midpoints of the dose intervals through week 24 compared with only 7.6% of patients in the placebo group (P < 0.0001) (Table 15).

Results from the pre-specified subgroup analyses of the primary end point by baseline BPI worst pain (≤ 6.0, > 6.0) were similar to those of the analysis for the overall population, demonstrating that in each of the subgroups, a notably greater percentage of patients in the burosumab group versus the placebo group achieved a serum phosphorus concentration above the LLN across the midpoints of the dose intervals through week 24 (Table 55).

Table 15: Patients Reaching Normal Range of Serum Phosphorus Concentration in Studies CL301, CL201, CL205, and CL303

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks	Placebo
Serum phosphorus concentration (mmol/L)						
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40, n (%)	17 (58.6)	1 (3.1)	17 (65.4)	10 (76.9)	NA	NA
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 64, n (%)	19 (65.5)	1 (3.1)	16 (66.7)	NR	NA	NA

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks	Placebo
Patients achieving mean serum phosphorus > LLN across midpoints of dose intervals through week 24 – n (%)	NR	NR	NR	NR	64 (94.1)	5 (7.6)
95% CI	NR	NR	NR	NR	(85.8 to 97.7)	(3.3 to 16.5)
P value	NR	NR	NR	NR	< 0.0001[a]	

CI = confidence interval; LLN = lower limit of normal; NR = not reported.

[a] The P value is from Cochran-Mantel-Haenszel testing for association between achieving mean serum phosphorus levels above the LLN and treatment group, adjusting for the actual randomization stratification of Brief Pain Inventory average pain and region.

Source: Clinical Study Reports for studies CL301, CL201, CL205, and CL303.[10-13]

TmP/GFR and TRP

Changes from baseline in TmP/GFR and TRP were secondary end points in the CL301, CL201, and CL303 studies.

Study CL301

In Study CL301, mean TmP/GFR increased in the burosumab group, from 0.71 (SD = 0.121) mmol/L at baseline to 1.08 (SD = 0.215) mmol/L at week 40 and 1.06 (SD = 0.209) mmol/L at week 64. Mean serum phosphorus concentrations in the active-control group decreased from 0.65 (SD = 0.107) mmol/L at baseline to 0.59 (SD = 0.113) mmol/L at week 40 and 0.61 (SD = 0.159) mmol/L at week 64. The difference in TmP/GFR between the burosumab group and the active-control group in change from baseline at week 40 was 0.44 mmol/L (95% CI, 0.36 to 0.52; P < 0.0001) in favour of burosumab, and at week 64, it was 0.40 mmol/L (95% CI, 0.31 to 0.50; P < 0.0001) in favour of burosumab (Table 51).

Of the 29 patients randomized to the burosumab treatment group, 23 patients (82.1%) and 21 patients (80.8%) achieved TmP/GFR within the normal range (0.84 mmol/L to 1.42 mmol/L) at week 40 and week 64, respectively. Of the 32 patients randomized to the active-control group (oral phosphate and active vitamin D therapy), only one patient (3.1%) achieved TmP/GFR within the normal range (0.84 mmol/L to 1.42 mmol/L) at week 40 and week 64 (Table 51).

In the burosumab group, mean TRP increased from 0.86 (SD = 0.065) at baseline to 0.90 (SD = 0.048) at week 40 and week 64. In the active-control group, mean TRP decreased from 0.85 (SD = 0.080) at baseline to 0.72 (SD = 0.109) at week 40 and to 0.73 (SD = 0.132) at week 64. The difference in TRP between the burosumab group and the active-control group in change from baseline at week 40 was 0.17 (95% CI, 0.13 to 0.21; P < 0.0001) in favour of burosumab, and at week 64, it was 0.15 (95% CI, 0.10 to 0.20; P < 0.0001) in favour of burosumab (Table 51).

Study CL201

In Study CL201, burosumab every two weeks increased mean TmP/GFR from 0.70 (SD = 0.159) mmol/L at baseline to 1.07 (SD = 0.195) mmol/L at week 40 and 1.08 (SD = 0.171) mmol/L at week 64. In the group receiving burosumab every two weeks,

84.0% of patients (21 out of 25) at week 40 and 90.5% of patients (19 out of 21) at week 64 had TmP/GFR values within the reference range (0.84 mmol/L to 1.42 mmol/L) (Table 53).

In the group receiving burosumab every two weeks, mean TRP was 0.86 (SD = 0.067) at baseline and increased to 0.90 (SD = 0.040) at week 40 and 0.91 (SD = 0.023) at week 64 (Table 53).

Study CL303

At baseline, the mean TmP/GFR was 1.68 (SD = 0.400; range = 1.0 to 3.4) mg/dL in the burosumab group and 1.60 (SD = 0.369; range = 0.7 to 2.6) mg/dL in the placebo group. At week 24, the mean TmP/GFR was 2.21 (SD = 0.483) mg/dL in the burosumab group and 1.73 (0.424) mg/dL in the placebo group. The LS mean difference between treatment groups in change from baseline at week 24 was 0.43 mg/dL (95% CI, 0.30 to 0.57; P < 0.0001) in favour of burosumab (Table 56).

At baseline, the mean TRP was 0.81 (SD = 0.083; range = 0.6 to 1.0) in the burosumab group and 0.81 (SD = 0.084; range = 0.5 to 0.9) in the placebo group. At week 24, the mean TRP was 0.84 (SD = 0.065) in the burosumab group and 0.80 (SD = 0.106) in the placebo group. The LS mean difference between treatment groups in change from baseline at week 24 was 0.04 (95% CI, 0.02 to 0.07; P = 0.0008) in favour of burosumab (Table 56).

Serum 1,25-Dihydroxyvitamin D

Change from baseline in $1,25(OH)_2D$ was a secondary end point in all of the included studies.

Study CL301

In the burosumab group, mean serum $1,25(OH)_2D$ concentrations increased from 110.4 (SD = 48.1) pmol/L at baseline to 174.2 (SD = 51.2) pmol/L at week 40. Serum $1,25(OH)_2D$ levels remained above the baseline mean value at week 64, with a mean of 129.8 (SD = 31.1) pmol/L. In the active-control group, mean serum $1,25(OH)_2D$ concentrations increased from 96.4 (SD = 35.7) pmol/L at baseline to 142.2 (SD = 46.8) pmol/L at week 40. Serum $1,25(OH)_2D$ levels remained above the baseline mean value at week 64, with a mean of 105.8 (SD = 32.8) pmol/L. The difference in serum $1,25(OH)_2D$ concentrations between the burosumab group and the active-control group in change from baseline at week 40 was 26.88 (95% CI, 2.34 to 51.42; P = 0.0318) in favour of burosumab, and at week 64 it was 20.91 (95% CI, 4.17 to 37.65; P = 0.0144) in favour of burosumab (Table 51).

Study CL201

In the group receiving burosumab every two weeks, mean serum $1,25(OH)_2D$ levels increased over time from 107.34 (SD = 57.115) pmol/L at baseline to 180.85 pmol/L (39.373 pmol/L) at week 40 and to 168.65 (SD = 42.532) pmol/L at week 64 (Table 53).

Study CL205

Treatment with burosumab every two weeks increased serum $1,25(OH)_2D$ levels from 116.6 (SD = 45.81) pmol/L at baseline to 136.2 (SD = 24.83) pmol/L at week 40. The change from baseline to week 40 was 19.38 pmol/L (95% CI, 3.37 to 35.39; P = 0.0177) (Table 53).

Study CL303

At baseline, the mean serum 1,25(OH)$_2$D concentration was 32.4 (SD = 12.96; range = 4 to 75) pg/mL in the burosumab group and 33.5 (SD = 15.61; range = 4 to 80) pg/mL in the placebo group (normal range: 18 pg/mL to 72 pg/mL). At week 22 (midpoint of dose interval), the mean serum 1,25(OH)$_2$D concentration had increased in the burosumab group to 57.0 (SD = 18.02 pg/mL). In the placebo group, the mean serum 1,25(OH)$_2$D concentration at week 22 was 34.9 (SD = 14.52) pg/mL. The LS mean difference between treatment groups in the change from baseline at week 22 was 22.73 pg/mL (95% CI, 18.08 to 27.38; P < 0.0001) in favour of burosumab (Table 56).

Alkaline Phosphatase and Bone-Specific Alkaline Phosphatase

Change from baseline in ALP was a secondary end point in studies CL301, CL201, and CL205. Change from baseline in BALP was a secondary end point in studies CL201 and CL303.

Study CL301

In Study CL301, mean serum ALP concentrations at baseline (517 [SD = 140] U/L) were well above the ULNs for the ages of the children in this study (297 U/L to 385 U/L, depending on the age and sex of the child). Serum ALP concentrations decreased in the burosumab group from 511 (SD = 125) U/L at baseline to 380.8 (SD = 99.46) U/L at week 40 and to 336.9 (SD = 86.13) U/L at week 64. Serum ALP concentrations decreased in the active-control group from 523.4 (SD = 154.42) U/L at baseline to 488.7 (SD = 189.07) U/L at week 40 and 495.4 (SD = 182.07) U/L at week 64. The difference between the groups in change in serum ALP concentration from baseline at week 40 was −95.95 (95% CI, −136.05 to −55.84; P < 0.0001) in favour of burosumab, and at week 64, it was −146.6 (95% CI, −191.61 to −101.52; P < 0.0001) in favour of burosumab (Table 51).

Study CL201

In the group receiving burosumab every two weeks, mean serum ALP levels were 461.9 (SD = 110.21) U/L at baseline, above the ULN ranges for the ages of the children in this study (approximately 297 U/L to 385 U/L, depending on the age and sex of the child). Similarly, for BALP, mean serum levels at baseline were 163.54 (SD = 58.610) mcg/L, well above the ULN ranges for the ages of the children in this study (approximately 23 mcg/L). Mean serum ALP levels decreased to 382.5 (SD = 88.03) U/L at week 40 and to 354.2 (SD = 73.37) U/L at week 64. Mean serum BALP levels decreased to 130.04 (SD = 38.923) mcg/L at week 40 and to 110.06 (SD = 31.194) mcg/L at week 64 (Table 53).

Study CL205

At baseline, mean serum ALP levels were 549 (SD = 193.8) U/L, above the ULN for the children in this study (approximately 297 U/L to 345 U/L, depending on the age and sex of the child). Mean serum ALP levels decreased to 335.4 (SD = 87.59) U/L at week 40. Change from baseline to week 40 was −213.08 U/L (95% CI, −239.59 to −186.56; P < 0.0001) (Table 53).

Eleven patients (85%) had serum ALP concentrations above the ULN for age and sex at baseline; all patients had decreases from baseline to week 40. Three patients (23%) had decreases from above the ULN for age and sex at baseline to within the reference range at week 40.

Study CL303

The mean BALP concentration at baseline was 24 (SD = 19.7) mcg/L in the burosumab group and 25 (SD = 17.3) mcg/L in the placebo group. At week 24, the mean BALP concentration was 30 (SD = 26.3) mcg/L in the burosumab group and 26 (SD = 17.3) mcg/L in the placebo group. The LS mean difference between treatment groups in change from baseline at week 24 was 4.06 mcg/L (95% CI, −0.75 to 8.87; P = 0.0983) (Table 56).

Brief Pain Inventory

In Study CL303, change from baseline in BPI worst pain score was a key secondary efficacy end point that was adjusted for multiple testing. Changes from baseline in BPI pain severity score and BPI pain interference score were additional secondary efficacy end points.

BPI Worst Pain

In Study CL303, the mean BPI worst pain scores at baseline were 6.8 (SD = 1.31; range = 3.0 to 8.9) and 6.5 (SD = 1.43; range = 3.1 to 9.1) for the burosumab and placebo groups, respectively. The mean for BPI worst pain score at week 24 in the burosumab group was 5.8 (SD = 1.92); in the placebo group, it was 6.1 (SD = 2.01). The LS mean difference between treatment groups at week 24 was −0.46 (95% CI, −1.00 to 0.08; P = 0.0919). This difference did not reach statistical significance after the Hochberg multiplicity adjustment, which required a P value ≤ 0.05 for significance for the key secondary end point with the largest P value (Table 57).

Subgroup analyses were conducted for BPI worst pain by baseline BPI worst pain (≤ 6.0, > 6.0), baseline WOMAC physical function score (≤ 47.8 [the baseline median score], > 47.8), baseline WOMAC stiffness score (≤ 62.5 [the baseline median score], > 62.5), presence of active fractures or pseudofractures at baseline (yes, no), and patients with history of bone fractures. Results of these analyses were consistent with results for the study population as a whole with regard to showing a favourable direction of effect of burosumab relative to placebo (Table 58).

BPI Pain Severity Score

In the CL303 study, at baseline, the mean BPI pain severity score was 5.2 (SD = 1.53; range = 1.8 to 8.3) in the burosumab group and 4.9 (SD = 1.55; range = 1.2 to 7.9) in the placebo group, which indicated moderate pain severity in this study population. At week 24, the burosumab group had an LS mean change from baseline of −0.59 (95% CI, −0.91 to −0.27), compared with an LS mean change from baseline of −0.16 (95% CI, −0.55 to 0.22) in the placebo group. The LS mean difference between treatment groups at week 24 was −0.43 (95% CI, −0.93 to 0.07; P = 0.0926) (Table 61).

BPI Pain Interference

In the CL303 study, at baseline, the mean BPI pain interference score was 5.2 (SD = 2.24; range = 0.1 to 10.0) in the burosumab group and 4.8 (SD = 2.17; range = 0.0 to 10.0) in the placebo group, which indicated moderate disruption in activities of daily living due to pain in this study population. At week 24, the burosumab group had an LS mean change from baseline of −0.40 (95% CI, −0.85 to 0.04), compared with an LS mean change of −0.27 (95% CI, −0.78 to 0.23) in the placebo group. The LS mean difference between treatment groups at week 24 was −0.13 (95% CI, −0.70 to 0.44; P = 0.6511) (Table 61).

Western Ontario and McMaster Universities Osteoarthritis Index

In the CL303 study, changes from baseline to week 24 in the WOMAC stiffness score and WOMAC physical function score were key secondary efficacy end points.

WOMAC Physical Function

In the CL303 study, at baseline, the mean WOMAC physical function scores on a normalized scale from 0 (best health state) to 100 (worst) were 50.8 (SD = 19.66; range = 7.4 to 91.2) and 43.9 (SD = 19.94; range = 0 to 97.1) for the burosumab and placebo groups, respectively. The mean for WOMAC physical function score at week 24 in the burosumab group was 43.4 (SD = 19.51); in the placebo group, it was 42.7 (SD = 22.76). The LS mean difference between treatment groups at week 24 was −4.90 (95% CI, −9.76 to −0.05; P = 0.0478). This difference did not reach statistical significance after the Hochberg multiplicity adjustment, which required a P value ≤ 0.025 for significance for the key secondary end point with the second-largest P value (Table 57).

Subgroup analyses were conducted for WOMAC physical function by baseline BPI worst pain (≤ 6.0, > 6.0), baseline WOMAC physical function score (≤ 47.8 [the baseline median score], > 47.8), baseline WOMAC stiffness score (≤ 62.5 [the baseline median score], > 62.5), presence of active fractures or pseudofractures at baseline (yes, no), and patients with history of bone fractures. Results of these analyses were consistent with results for the study population as a whole with regard to showing a favourable direction of effect of burosumab relative to placebo (Table 59).

WOMAC Stiffness Score

In the CL303 study, at baseline, the mean WOMAC stiffness scores on a normalized scale from 0 (best health state) to 100 (worst) were 64.7 (SD = 20.25; range = 12.5 to 100.0) and 61.4 (SD = 20.77; range = 0 to 100.0) for the burosumab and placebo groups, respectively. The mean for WOMAC stiffness score at week 24 in the burosumab group was 53.7 (SD = 20.76); in the placebo group, it was 60.4 (SD = 21.83). The LS mean difference between treatment groups at week 24 was −8.31 (95% CI, −14.68 to −1.94; P = 0.0106). This difference was statistically significant after the Hochberg multiplicity adjustment, which required a P value ≤ 0.0167 for significance for the key secondary end point with the smallest P value (Table 57).

Subgroup analyses were conducted for WOMAC stiffness score by baseline BPI worst pain (≤ 6.0, > 6.0), baseline WOMAC physical function score (≤ 47.8 [the baseline median score], > 47.8), baseline WOMAC stiffness score (≤ 62.5 [the baseline median score], > 62.5), presence of active fractures or pseudofractures at baseline (yes, no), and patients with history of bone fractures. Results of these analyses were consistent with results for the study population as a whole with regard to showing a favourable direction of effect of burosumab relative to placebo (Table 60).

Brief Fatigue Inventory

Change from baseline BFI worst fatigue score and in BFI global fatigue score were additional secondary efficacy end points in Study CL303.

BFI Worst Fatigue Score

In the CL303 study, the mean BFI worst fatigue score at baseline was 6.9 (SD = 1.66; range = 2.8 to 9.8) in the burosumab group and 6.7 (SD = 1.53; range = 3.6 to 9.9) in the

placebo group. At week 24, the burosumab group had an LS mean change from baseline of −0.67 (95% CI, −1.21 to −0.12), compared with an LS mean change of −0.47 (95% CI, −1.03 to 0.09) in the placebo group. The LS mean difference between treatment groups at week 24 was −0.20 (95% CI, −0.80 to 0.40; P = 0.5150) (Table 61).

BFI Global Fatigue Score

In the CL303 study, the mean BFI global fatigue score at baseline was 5.4 (SD = 2.04; range = 1.2 to 8.8) in the burosumab group and 4.9 (SD = 1.93; range = 0.7 to 9.0) in the placebo group. At week 24, the burosumab group had an LS mean change from baseline of 0.04 (95% CI, −0.48 to 0.57), compared with an LS mean change of −0.07 (95% CI, −0.66 to 0.53) in the placebo group. The LS mean difference between treatment groups at week 24 was 0.11 (95% CI, −0.46 to 0.67; P = 0.7129) (Table 61).

Faces Pain Scale – Revised

Change from baseline in the FPS-R was a secondary end point in the CL301 study.

In the CL301 study, pain intensity was self-reported by patients greater than or equal to five years of age at the screening visit (15 patients in the burosumab group and 20 patients in the active-control group) using the FPS-R (where 0 = no hurt and 10 = hurts worst; even numbers only). The FPS-R is a rating of pain intensity at rest and not during or immediately after physical activity. The median FPS-R score was 0 at baseline and at weeks 40 and 64. Mean FPS-R scores were similar in the burosumab and active-control groups at baseline (0.4 [SD = 1.12] and 0.7 [SD = 1.17], respectively). The difference between the burosumab group and the active-control group in change from baseline at week 40 was −0.00 (95% CI, −0.80 to 0.79; P = 0.9905), and at week 64, it was 0.05 (95% CI, −0.58 to 0.68; P = 0.8786), indicating no notable change between treatment groups (Table 62).

6-Minute Walk Test

Change from baseline in the 6MWT total distance and percentage of predicted normal was a secondary efficacy end point in the CL301 and CL201 studies, and an exploratory efficacy end point in Study CL303.

Study CL301

In Study Cl301, the 6MWT was not administered to patients less than five years of age at the screening visit; nor was it administered to these patients when they were greater than or equal to five years of age at post-baseline visits. Walking ability was evaluated as the total distance walked in the 6MWT and as the percentage of predicted 6MWT values based on published normative data based on age, gender, and height.

In the burosumab group, mean 6MWT distance walked increased from 385 (SD = 86) m at baseline to 435 (SD = 86) m at week 40 and 466 (SD = 82) m at week 64. In the active-control group, the mean 6MWT distance walked was 451 (SD = 106) m at baseline, 457 (SD = 96) m at week 40, and 481 (SD = 113) m at week 64. The difference in 6MWT distance walked between the treatment groups at week 40 was 43 m (95% CI, −0.3 to 87; P = 0.0514), and at week 64, it was 46 m (95% CI, 2 to 89; P = 0.0399) (Table 63).

In the burosumab group, mean 6MWT percentages of predicted normal values increased from 65.1 (SD = 12.1) at baseline to 71.6 (SD = 12.8) at week 40 and 75.5 (SD = 11.6) at week 64. In the active-control group, mean 6MWT percentages of predicted normal values were 76.2 (SD = 14.8) at baseline, 75.3 (SD = 14.2) at week 40, and 78.1 (SD = 17.5) at

week 64. The difference between the treatment groups in 6MWT percentage of predicted normal values at week 40 was 6.7 percentage points (95% CI, −0.4 to 13.8; P = 0.0633); at week 64, it was 7.3 percentage points (95% CI, 0.01 to 14.5; P = 0.0496) (Table 63).

Study CL201

In the group receiving burosumab every two weeks, the mean 6MWT distance walked increased from 480 (SD = 84.80) m at baseline to 534 (SD = 58.70) m at week 64. The LS mean for the change from baseline at week 64 was 52.67 m (95% CI, 35.39 to 69.95; P < 0.0001) (Table 64).

The mean distance walked, as a percentile of predicted values using published, normative data based on gender, age, and height, also increased from 79.32% (SD = 13.257%) at baseline to 85% (SD = 10.326%) at week 64. The LS mean for the change from baseline at week 64 was 5.29% (95% CI, 2.22 to 8.36; P = 0.0007) (Table 64).

In a planned analysis, 6MWT results were analyzed by subgroups based on baseline percentage of predicted 6MWT (< 80% [abnormal] or ≥ 80% [normal range]) to assess the effect of burosumab on patients with, respectively, the greater and lesser impairment in mobility at baseline. In the less than 80% baseline predicted 6MWT subgroup, the distance walked in the 6MWT increased from a mean of 425 m at baseline to 510 m at week 64. The LS mean for the change from baseline at week 64 was 95.54 m (95% CI, 72.02 to 119.06; P < 0.0001). In the greater than or equal to 80% baseline predicted 6MWT subgroup, the distance walked in the 6MWT increased from a mean of 544 m at baseline to 562 m at week 64. The LS mean for the change from baseline at week 64 was 16.88 m (95% CI, −7.67 to 41.44; P = 0.1777) (Table 64).

6MWT results were also analyzed by subgroups based on baseline rickets severity (RSS total score < 1.5 versus ≥ 1.5). Results in these subgroups were similar to those of the overall study population (Table 64).

Study CL303

In the CL303 study, at baseline, the mean actual distance walked was 356.8 (SD = 109.46; range = 55 to 643) m in the burosumab group and 367.4 (SD = 103.41; range = 160 to 615) m in the placebo group. At week 24, the mean actual distance walked was 381.5 (SD = 108.46) m in the burosumab group and 369.4 (SD = 103.39) m in the placebo group. The LS mean difference between treatment groups for the change from baseline to week 24 was 19.93 m (95% CI, 4.38 to 35.49; P = 0.0120) in favour of burosumab (Table 65).

At baseline, the mean percentage predicted distance walked was 51.4% (SD = 15.83%; range = 7.6% to 92.4%) in the burosumab group and 52.3% (SD = 14.90%; range = 23.1% to 88.4%) in the placebo group. At week 24, the mean percentage of predicted distance walked was 55.2% (SD = 15.86%) in the burosumab group and 52.4% (SD = 14.33%) in the placebo group. The LS mean difference between treatment groups for the change from baseline to week 24 was 3.19% (95% CI, 0.98 to 5.41; P = 0.0047) in favour of burosumab (Table 65).

PROMIS Scores for Pediatric Pain Interference, Fatigue, and Physical Function Mobility Scales

In Study CL301, the PROMIS pain interference, physical function mobility, and fatigue questionnaires were administered to patients aged greater than or equal to five years. Domain summary scores are t scores with a mean of 50 and an SD of 10. Higher t scores

represent greater impact of the construct being measured; accordingly, beneficial effects are indicated by increases in mobility scores and decreases in pain and fatigue scores. Changes from baseline in the PROMIS scores in pediatric pain interference, physical function mobility, and fatigue domains were secondary end points in the CL301 study.

In CL301, the mean pain interference t score in the burosumab group was 53.1 (SD = 10.95) at baseline, 47.6 (SD = 9.84) at week 40, and 49.3 (SD = 8.07) at week 64. In the active-control group, the mean pain interference t score was 49.9 (SD = 12.05) at baseline, 50.4 (SD = 9.51) at week 40, and 49.4 (SD = 9.52) at week 64. The difference between the groups in change in pain interference t scores to week 40 was −5.02 (95% CI, −9.29 to −0.75; P = 0.0212), indicating more reduction in pain in the burosumab treatment group than in the active-control group. The difference between the treatment groups was smaller at week 64 than it was at week 40, where it was −2.26 (95% CI, −6.61, 2.09; P = 0.3091) (Table 66).

The mean physical function mobility t score in the burosumab group was 45.2 (SD = 9.05) at baseline, 47.9 (SD = 8.32) at week 40, and 47.9 (SD = 9.24) at week 64. In the active-control group, the mean physical function mobility t score was 45.5 (SD = 9.86) at baseline, 45.5 (SD = 9.71) at week 40, and 46.3 (SD = 9.63) at week 64. The difference between the groups in change in physical function mobility t scores to week 40 was 2.68 (95% CI, −0.52 to 5.89; P = 0.1009), and at week 64 it was 1.90 (95% CI, −1.80 to 5.59; P = 0.3145) (Table 66).

The mean fatigue t score in the burosumab group was 48.8 (SD = 9.60) at baseline, 44.7 (SD = 10.49) at week 40, and 45.2 (SD = 10.69) at week 64. In the active-control group, the mean fatigue t score was 47.0 (SD = 13.70) at baseline, 46.6 (SD = 10.73) at week 40, and 45.0 (SD = 11.17) at week 64. The difference between the groups in change in fatigue t scores to week 40 was −3.25 (95% CI, −7.86 to 1.37; P = 0.1676), and at week 64 it was −1.08 (95 % CI, −6.21 to 4.06; P = 0.6810) (Table 66).

Pediatric Orthopaedic Society of North America – Pediatric Outcomes Data Collection Instrument

Changes from baseline in the POSNA-PODCI sports and physical functioning scale and PODCI pain and comfort scale were secondary end points in the CL201 study. The POSNA-PODCI questionnaire was used to measure the impact of bone and muscle conditions on daily activities and HRQoL.

The LS mean for the change from baseline to week 64 in sports and physical functioning was 7.74 (95% CI, 2.58 to 12.91; P = 0.0033), while the LS mean for the change from baseline to week 64 in pain and comfort was 5.60 (95% CI, −0.09 to 11.30; P = 0.0536) (Table 67).

POSNA-PODCI scale scores were analyzed by predefined subgroups based on RSS total score at baseline (≥ 1.5 or < 1.5) and by predefined subgroups based on POSNA-PODCI global functioning scale scores at baseline (scores < 40 [abnormal] or ≥ 40 [normal range]). Patients in the higher RSS subgroup had lower scores at baseline (greater functional disability and pain) and showed greater improvements with burosumab treatment than patients in the lower RSS subgroup (Table 67). In the subgroup of patients with RSS total scores of less than 1.5, the mean scores at baseline for the physical functioning scale and pain and comfort scale were 42.7 (SD = 15.38) and 46.3 (SD = 11.92), respectively. The LS mean for the change from baseline to week 64 in sports and physical functioning was 6.12 (95% CI, 3.56 to 8.69; P < 0.0001), while the LS mean for the change from baseline to

week 64 in pain and comfort was −3.87 (95% CI, −12.81 to 5.07; P = 0.3963). In the subgroup of patients with an RSS total score of greater than or equal to 1.5, the mean scores at baseline for the physical functioning scale and pain and comfort scale were 30.3 (SD = 14.51) and 29.4 (SD = 13.67), respectively. The LS mean for the change from baseline to week 64 in sports and physical functioning was 8.62 (95% CI, 0.98 to 16.25; P = 0.0270), while the LS mean for the change from baseline to week 64 in pain and comfort was 10.57 (95% CI, 3.71 to 17.44; P = 0.0025). Similarly, patients in the lower global functioning subgroup (< 40) showed lower scores at baseline and greater improvements with treatment than patients in the higher (≥ 40) global functioning subgroup (Table 67).

The Bruininks-Oseretsky Test of Motor Proficiency – Second Edition

The change from baseline in the BOT-2 subtests for running speed and agility and for strength were exploratory efficacy end points in the CL201 study.

At baseline, mean subtest scaled scores were 11.1 (SD = 4.85) for running speed and agility and 14.2 (SD = 5.00) for strength. The mean strength and agility composite standard score was 43.9 (SD = 9.39) (Table 68).

The mean running speed/agility subtest scaled score increased to 14.2 (SD = 4.09) at week 64. A similar pattern was observed for the strength subtest; the mean scaled score increased to 15.1 (SD = 5.26) by week 64, indicating improved strength. The strength and agility composite score increased to 48.3 (SD = 10.95) at week 64 (Table 68). No statistical significance test for comparison with the treatment group was conducted.

Short Form (10) for Children Health Survey

Change from baseline in the SF-10 PHS and PSS were exploratory efficacy end points in the CL301 and CL201 studies. In the CL301 study, only patients who were at least five years of age at the time of the screening visit completed this questionnaire. The SF-10 assess overall HRQoL. Responses were used to generate two component summary scores: the PHS and PSS. Scale scores are standardized to a mean of 50 and an SD of 10 in the combined US general population. Higher global scores are associated with better quality of life.

Study CL301

In the CL301 study, at baseline, mean scores for the PHS were approximately one SD below the population mean in both treatment groups (burosumab: 40.03 [SD = 10.07]; active-control group: 40.74 [SD = 15.30]), indicating mild impairment in reported physical health in comparison with the US general population. The mean PHS score in the burosumab group was 46.16 (SD = 9.90) at week 40 and 46.12 (SD = 9.84) at week 64, reflecting changes from baseline of 6.13 (SD = 7.93) and 6.08 (SD = 8.47), respectively. In the active-control group, the mean PHS score was 42.27 (SD = 12.51) at week 40 and 41.07 (SD = 15.09) at week 64, representing changes of 1.54 (SD = 12.21) and 0.33 (SD = 10.81), respectively (Table 69). No statistical significance test for comparison between the two treatment groups was conducted.

At baseline, mean scores for the PSS were near the standardized mean of 50 in both treatment groups (burosumab group: 50.76 [SD = 9.65]; active-control group: 52.79 [SD = 9.40]), indicating no impairment in psychosocial function in comparison with the US general population. In the burosumab group, the mean PSS score was 52.66 (SD = 9.22) at week 40 and 52.06 (SD = 9.14) at week 64, representing changes of 1.90 (SD = 6.73) and

1.31 (SD = 8.18), respectively. In the active-control group, the mean PSS score was 51.85 (SD = 9.33) at week 40 and 53.95 (SD = 8.46) at week 64, representing changes of −0.94 (SD = 6.79) and 1.16 (SD = 6.24), respectively (Table 69).

Study CL201

In the CL201 study, the means for the PHS were 41.6 (SD = 12.1) at baseline, 49.2 (SD = 8.2) at week 40, and 47.4 (SD = 10.4) at week 64, with changes from baseline of 6.8 (SD = 13.2) at week 40 and 47.4 (SD = 10.4) at week 64. (Table 70). The means for the PSS were 53.4 (SD = 9.5) at baseline, 55.8 (SD = 8.5) at week 40, and 52.9 (SD = 8.5) at week 64, with changes from baseline of 1.3 (SD = 7.9) at week 40 and −0.52 (SD = 7.8) at week 64. (Table 70). Mean physical scores showed improvement with treatment, whereas mean psychosocial scores showed only slight changes. No statistical significance test for comparison with the treatment group was conducted.

Dental Assessments

Dental assessment was only conducted in Study CL301. At each clinic visit, an oral examination was conducted, and patients were asked proactively if they had experienced any of the following specific dental events since their last visit: dental abscess, tooth extraction (due to abscess or decay), root canal, dental cavities (caries), or gingivitis.

Overall, at post-baseline visits to week 64, dental conditions were reported for 12 out of 29 patients (41%) in the burosumab group and five out of 32 patients (16%) in the active-control group (Table 71). For both groups, most of the dental complications occurred in deciduous teeth, not permanent teeth. Of the patients with dental conditions at post-baseline, seven out of 12 in the burosumab group and three out of five in the active-control group had a history of dental abscesses, excessive cavities, root canal, and/or tooth extractions. No statistical significance test for comparison between the two treatment groups was conducted.

Fractures and Pseudofractures

Fractures and pseudofractures were assessed in the CL303 study only. At baseline, patients in the burosumab group had 14 active fractures and 51 active pseudofractures, and patients in the placebo group had 13 active fractures and 78 active pseudofractures. At week 24, 50.0% of baseline active fractures in the burosumab group were graded as fully healed, compared with 0.0% in the placebo group. Similarly, at week 24, 41.2% of baseline active pseudofractures in the burosumab group were graded as fully healed, compared with 9.0% in the placebo group (Table 72). No statistical significance test for comparison between the two treatment groups was conducted.

Harms

Only those harms identified in the review protocol are reported here. See Table 16 for detailed harms data.

Adverse Events

The overall frequency of TEAEs was similar between studies for those who received burosumab. AEs were reported by all patients who received burosumab in studies CL301, CL201, and CL205, and by 94.1% of patients who received burosumab in Study CL303. In Study CL301, 84% of patients (27 out of 32) in the active-control group experienced at least

one TEAE. In Study CL303, 92.4% of the patients (61 out of 66) in the placebo group experienced at least one TEAE (Table 16).

In Study CL301, among the most commonly reported TEAEs were pyrexia (55% in the burosumab group, 19% in the active-control group); cough (52% in the burosumab group, 19% in the active-control group); vomiting (41% in the burosumab group, 25% in the active-control group); headache (35% in the burosumab group, 19% in the active-control group); diarrhea (24% in the burosumab group, 6% in the active-control group); and nasopharyngitis (38% in the burosumab group, 44% in the active-control group). Also among the most commonly reported TEAEs were arthralgia (45% in the burosumab group, active-control: 31%); pain in extremity (38% in the burosumab group, 21% in the active-control group); tooth abscess (28% in the burosumab group, 9% in the active-control group); vitamin D decrease (21% in the burosumab group, 3% in the active-control group); ISR (24% in the burosumab group, 0% in the active-control group); and injection-site erythema (31% in the burosumab group, 0% in the active-control group) (Table 16).

In Study CL201, the most frequent TEAEs (> 30% incidence) in the group receiving burosumab every two weeks were headache (69.2%), cough (65.4%), injection-site erythema (46.2%), nasopharyngitis (42.3%), pain in extremity (38.5%), vomiting (38.5%), ISR (38.5%), upper respiratory tract infection (38.5%), pyrexia (34.6%), arthralgia (30.8%), and oropharyngeal pain (30.8%) (Table 16).

In Study CL205, the most frequent TEAEs (> 30% incidence [four or more of 13 patients]) were cough (76.9%), pyrexia (61.5%), upper respiratory tract infection (53.8%), vomiting (46.2%), rhinorrhea (38.5%), diarrhea (30.8%), and streptococcal pharyngitis (30.8%) (Table 16).

In Study CL303, the most commonly (≥ 10%) reported TEAEs in the burosumab group were back pain (14.7%), nasopharyngitis (13.2%), headache (13.2%), tooth abscess (13.2%), restless legs syndrome (11.8%), nausea (10.3%), and dizziness (10.3%). The most commonly (≥ 10%) reported TEAEs in the placebo group were arthralgia (24.2%), pain in extremity (15.2%), and oropharyngeal pain (10.6%) (Table 16).

Serious Adverse Events

In Study CL301, three patients (10%) in the burosumab group experienced SAEs (craniosynostosis, viral infection, and migraine), and three (9%) in the active-control group experienced SAEs (hematuria, craniosynostosis, and knee deformity) (Table 16). These events required hospitalization and were mild or moderate in severity, with the exception of the craniosynostosis in the active-control group, which was considered severe. None of these events were assessed as related to study drug by the investigators.

In Study CL201, no patient in the group receiving burosumab every two weeks experienced an SAE (Table 16).

In Study CL205, one patient in the group receiving burosumab every two weeks experienced an SAE of tooth abscess (right maxillary buccal and canine space abscess) (Table 16). The patient was a four-year-old boy with XLH at the time of the event who had a relevant medical history of tooth abscess (approximately 14 months before the SAE). The event of tooth abscess was considered moderate in severity and unlikely to be related to burosumab.

In Study CL303, in the placebo-controlled treatment period (through week 24), four patients experienced serious TEAEs; none of these events were assessed by the investigator as related to study drug. In the burosumab group, two patients (2.9%) experienced serious TEAEs (irritable bowel syndrome, back pain). In the placebo group, two patients (3.0%) experienced serious TEAEs (upper respiratory tract infection, invasive ductal breast carcinoma) (Table 16).

Withdrawals Due to Adverse Events

In all of the included studies, no patient withdrew from treatment or from the studies due to AEs (Table 16).

Mortality

No deaths were reported during studies CL301, CL201, CL205, or CL303 (Table 16).

Notable Harms

In Study CL301, 15 patients in the burosumab group (52%) experienced ISRs. All events were mild in severity except for one event of moderate injection-site rash. All ISRs were considered related to study drug by the investigators except for two events (injection-site erosion and injection-site erythema). ISRs were not associated with any severe hypersensitivity reactions, and generally represented localized irritation that was not treated; most lasted approximately one to two days. Hypersensitivity TEAEs were experienced by 11 patients (38%) in the burosumab group and six patients (19%) in the active-control group. None of these events were categorized as serious TEAEs. In the burosumab group, all events were mild except for two moderate events (injection-site rash and generalized rash). Events of injection-site rash, injection-site urticaria, injection-site hypersensitivity, and generalized rash were considered by the investigators to be definitely related to burosumab. Events of rash, allergic dermatitis, allergic rhinitis, eczema, drug eruption, hypersensitivity, erythematous rash, and swelling of the face were considered by the investigators to be unrelated to burosumab. In the active-control group, the most frequent hypersensitivity TEAE was rash (two patients [6%]). All of the hypersensitivity events were mild, except for one moderate event (rash). All hypersensitivity events in the active-control group were considered by the investigators to be unrelated to the study drug. No TEAEs of hyperphosphatemia, ectopic mineralization, or restless leg syndrome were reported in either treatment group.

In Study CL201, 19 patients (73.1%) in the group receiving burosumab every two weeks experienced TEAEs of ISR; all events were mild in severity. ISRs were considered related to treatment by the investigators for 15 patients (57.7%). The duration of most ISRs was approximately one to two days; a majority of patients who experienced an ISR had only one or two occurrences. ISRs were not associated with any severe hypersensitivity reactions and generally represented localized irritation. Ten patients (38.5%) experienced hypersensitivity AEs. The most frequent hypersensitivity AEs (experienced by > one patient) were rash (26.9%) and injection-site rash (7.7%). All hypersensitivity AEs were mild or moderate. Most events of rash had durations of one to seven days. Overall, hypersensitivity AEs were considered related to treatment for four patients (15.4%). One patient experienced an AE of ectopic mineralization. That patient experienced a TEAE of moderate nephrocalcinosis, considered possibly related to treatment, that was noted at the week 40 visit. The event had not resolved as of the week 88 visit; however, the week 88 renal ultrasound assessment demonstrated the absence of nephrocalcinosis. No TEAEs of

hyperphosphatemia or restless leg syndrome were reported in the group receiving burosumab every two weeks.

In Study CL205, three patients (23.1%) experienced TEAEs of ISRs; one patient experienced injection-site erythema; one patient experienced injection-site pruritus; and one patient experienced ISR. All events were mild in severity and resolved in one or two days without treatment. ISRs were not associated with any severe hypersensitivity reactions and generally represented localized irritation. Four patients (30.8%) experienced potential hypersensitivity TEAEs. All four were mild and considered unrelated or unlikely to be related to burosumab. One patient experienced a TEAE of mild swelling of the face concurrently with a TEAE of mild pyrexia in the context of an SAE of moderate tooth abscess leading to hospitalization; all events were considered unlikely to be related to burosumab. One patient experienced a TEAE of mild urticaria that was considered unrelated to burosumab; one patient experienced a TEAE of mild rash on the hips and back that was considered unlikely to be related to burosumab; and one patient experienced a TEAE of mild hypersensitivity (environmental allergies) that was considered unrelated to burosumab. No TEAEs of hyperphosphatemia, ectopic mineralization, or restless leg syndrome were reported in the group receiving burosumab every two weeks.

In Study CL303, eight patients (11.8%) in the burosumab group and eight patients (12.1%) in the placebo group experienced TEAEs of ISRs. All ISRs were mild or moderate in severity; none were considered serious TEAEs. Hypersensitivity were reported for four patients (burosumab: 5.9%; placebo: 6.1%) in each treatment group. Three patients (4.5%) in the placebo group had rash. Other events reported for one patient each in either treatment group were contact dermatitis, eczema, injection-site rash, contact urticaria, and urticaria. Most hypersensitivity TEAEs were assessed as probably not related to the study drug; only injection-site rash was considered probably related. TEAEs of hyperphosphatemia were reported for four patients (5.9%) in the burosumab group and no patients in the placebo group. All hyperphosphatemia TEAEs were assessed by the investigator as mild in severity; none were considered serious TEAEs or led to discontinuation of study drug. A total of four patients (3%) (two in each treatment group) entered the study with a documented medical history of restless leg syndrome. Throughout the placebo-controlled treatment period, a total of eight patients (11.8%) in the burosumab group and five patients (7.6%) in the placebo group had a TEAE of restless leg syndrome or limb discomfort (13.5). Two of the four patients (one in each treatment group) with a prior history of restless leg syndrome experienced worsening of restless leg syndrome reported as a TEAE. All restless leg syndrome events were mild or moderate in severity, and most were considered related to the study drug (burosumab or placebo); no restless leg syndrome event was considered a serious TEAE. No TEAEs of ectopic mineralization were reported in either treatment group during the double-blind period.

Table 16: Summary of Harms

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Patients with ≥ 1 adverse event						
n (%)	29 (100)	27 (84.4)	26 (100.0)	13 (100)	64 (94.1)	61 (92.4)
Most common events[a]						
Pyrexia	16 (55.2)	6 (18.8)	9 (34.6)	8 (61.5)		
Injection-site erythema	9 (31.0)	0 (0.0)	12 (46.2)	1 (7.7)	3 (4.4)	2 (3.0)
Injection-site reaction	7 (24.1)	0 (0.0)	10 (38.5)	1 (7.7)	2 (2.9)	2 (3.0)
Injection-site pruritus	3 (10.3)	0 (0.0)	2 (7.7)	1 (7.7)	1 (1.5)	0
Injection-site swelling	3 (10.3)	0 (0.0)	5 (19.2)	0		
Injection-site rash	3 (10.3)	0 (0.0)	2 (7.7)	0	1 (1.5)	0
Vomiting	12 (41.4)	8 (25.0)	10 (38.5)	6 (46.2)		
Dental caries	9 (31.0)	2 (6.3)	0	0		
Diarrhea	7 (24.1)	2 (6.3)	5 (19.2)	4 (30.8)	5 (7.4)	5 (7.6)
Constipation	5 (17.2)	0 (0.0)	2 (7.7)	1 (7.7)	6 (8.8)	0
Nausea	3 (10.3)	1 (3.1)	5 (19.2)	1 (7.7)	7 (10.3)	6 (9.1)
Toothache	4 (13.8)	1 (3.1)	5 (19.2)	2 (15.4)		
Abdominal pain upper	3 (10.3)	3 (9.4)	4 (15.4)	2 (15.4)		
Nasopharyngitis	11 (37.9)	14 (43.8)	11 (42.3)	2 (15.4)	9 (13.2)	6 (9.1)
Tooth abscess	8 (27.6)	3 (9.4)	3 (11.5)	3 (23.1)	9 (13.2)	5 (7.6)
Influenza	4 (13.8)	6 (18.8)	3 (11.5)	0		
Upper respiratory tract infection	3 (10.3)	3 (9.4)	10 (38.5)	7 (53.8)	4 (5.9)	6 (9.1)
Cough	15 (51.7)	6 (18.8)	17 (65.4)	10 (76.9)		
Rhinorrhea	7 (24.1)	2 (6.3)	4 (15.4)	5 (38.5)	4 (5.9)	3 (4.5)
Nasal congestion	5 (17.2)	1 (3.1)	7 (26.9)	3 (23.1)		
Oropharyngeal pain	5 (17.2)	1 (3.1)	8 (30.8)	1 (7.7)	1 (1.5)	7 (10.6)
Asthma	4 (13.8)	1 (3.1)	2 (7.7)	0		
Arthralgia	13 (44.8)	10 (31.3)	8 (30.8)	3 (23.1)	6 (8.8)	16 (24.2)
Pain in extremity	11 (37.9)	10 (31.3)	10 (38.5)	3 (23.1)	5 (7.4)	10 (15.2)
Headache	10 (34.5)	6 (18.8)	18 (69.2)	1 (7.7)	9 (13.2)	5 (7.6)
Rash	3 (10.3)	2 (6.3)	7 (26.9)	1 (7.7)		
Contusion	4 (13.8)	0 (0.0)	3 (11.5)	1 (7.7)		
Fall	3 (10.3)	0 (0.0)	1 (3.8)	1 (7.7)		
Ear pain	4 (13.8)	1 (3.1)	4 (15.4)	2 (15.4)		

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Vitamin D decreased	6 (20.7)	1 (3.1)	5 (19.2)	1 (7.7)		
Vitamin D deficiency	5 (17.2)	1 (3.1)	2 (7.7)	0	5 (7.4)	3 (4.5)
Seasonal allergy	4 (13.8)	2 (6.3)	5 (19.2)	0		
Pharyngitis, streptococcal	1 (3.4)	1 (3.1)	3 (11.5)	4 (30.8)		
Viral upper respiratory tract infection	0	2 (6.3)	4 (15.4)	2 (15.4)		
Viral infection	2 (6.9)	1 (3.1)	3 (11.5)	1 (7.7)		
Abdominal discomfort	2 (6.9)	2 (6.3)	4 (15.4)	2 (15.4)		
Mouth ulceration	1 (3.4)	0	3 (11.5)	0		
Epistaxis	1 (3.4)	1 (3.1)	4 (15.4)	1 (7.7)		
Migraine	1 (3.4)	2 (6.3)	3 (11.5)	0		
Back pain	2 (6.9)	3 (9.4)	3 (11.5)	0	10 (14.7)	6 (9.1)
Thermal burn	1 (3.4)	0	3 (11.5)	0		
Respiratory tract congestion	0	1 (3.1)	0	2 (15.4)		
Skin abrasion	1 (3.4)	1 (3.1)	2 (7.7)	3 (23.1)		
Hypersomnia	0	0	0	2 (15.4)		
Restless legs syndrome	0	0	0	0	8 (11.8)	4 (6.1)
Dizziness	1 (3.4)	0	2 (7.7)	0	7 (10.3)	4 (6.1)
Patients with ≥ 1 serious adverse event						
n (%)	3 (10.3)	3 (9.4)	0	1 (7.7%)	2 (2.9)	2 (3.0)
Most common events						
Craniosynostosis	1 (3.4)	1 (3.1)	0	0	0	0
Viral infection	1 (3.4)	0	0	0	0	0
Migraine	1 (3.4)	0	0	0	0	0
Knee deformity	0	1 (3.1)	0	0	0	0
Hematuria	0	1 (3.1)	0	0	0	0
Tooth abscess (right maxillary buccal and canine space abscess)	0	0	0	1 (7.7%)	0	0
Irritable bowel syndrome	0	0	0	0	1 (1.5)	0
Back pain	0	0	0	0	1 (1.5)	0

	Study CL301		Study CL201	Study CL205	Study CL303	
	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Upper respiratory tract infection	0	0	0	0	0	1 (1.5)
Invasive ductal breast carcinoma	0	0	0	0	0	1 (1.5)
Patients who stopped treatment due to adverse events						
n (%)	0	0	0	0	0	0
Deaths						
n (%)	0	0	0	0	0	0
Notable harms n (%)						
Hyperphosphatemia	0	0	0	0	4 (5.9)	0
Ectopic mineralization	0	0	1 (3.8)	0	0	0
Hypersensitivity	11 (37.9)	6 (18.8)	10 (38.5)	4 (30.8)	4 (5.9)	4 (6.1)
Injection-site reactions	15 (51.7)	0	10 (38.5)	19 (73.1)	8 (11.8)	8 (12.1)
Headache	10 (34.5)	6 (18.8)	18 (69.2)	1 (7.7)	9 (13.2)	5 (7.6)
Restless leg syndrome	0	0	0	0	8 (11.8)	5 (7.6)

[a] Frequency > 10%.

Source: Clinical Study Reports for studies CL301, CL201, CL205, and CL303.[10-13]

Critical Appraisal

Internal Validity

Studies CL301 and CL303 used accepted methods to conceal allocation and randomize patients to treatments; the patients' characteristics appear to be balanced at baseline between groups within studies, with no major differences observed between treatment groups.

Given that studies CL301, CL201, and CL205 were open-label, patients were aware of the treatment allocation. As a result, the evaluation of patient-reported outcomes (such as the scales measuring pain, fatigue, or HRQoL) or AEs may have been affected by the unblinded treatment regimen because reporting bias could have been introduced, particularly for the within-group comparison to baseline. The effects of treatment on those subjective outcomes may have been overestimated as a consequence of patients' expectations. On the other hand, the assessments of RSS and RGI-C were conducted by radiologists who were blinded to patient identity, patient treatment status, and the timing of the radiographs; these factors would limit investigator bias for these two outcomes.

Except for Study CL303, which included the change from baseline to week 24 in BPI worst pain, WOMAC stiffness, and WOMAC physical function scores when adjusting for multiple testing, there was no control for multiplicity among the other secondary outcomes analyzed or among all secondary outcomes in studies CL301, CL201, and CL205. Consequently, results for these end points should be interpreted with consideration of the potential for inflated type I error.

Studies CL201 and CL205 were hypothesis-generating as opposed to hypothesis-testing. Study CL201, in particular, was a phase II, dose-finding study that did not have a non-burosumab comparator arm. The results from these studies could be supportive of the other phase III study (CL301), but cannot offer solid evidence of treatment benefits.

The absence of comparator groups in studies CL201 and CL205 makes it challenging to interpret small changes from baseline, especially where maturation may be responsible for changes in certain relevant outcomes, such as growth and the 6MWT.

There was a lack of data imputation of the patient-reported outcomes data when missing; such missing data are unlikely to be missing at random (usually sicker patients are missing). This could lead to overestimates of HRQoL. On the other hand, missing data were not common in the included studies; therefore, the results are unlikely to be affected by lack of imputation.

In Study CL301, the patient-reported outcomes FPS, PROMIS, and 6MWT were only conducted in patients whose age at baseline was at least five years (15 patients in the burosumab group and 20 patients in the active-control group). These very small sample sizes mean that strong inferences cannot be drawn about any between-group differences.

In Study CL205, the sample size was very small (only 13 patients were enrolled). As a result, differences in one or two patients can have a substantial impact on results, leading to a high degree of uncertainty about the differences observed due to random variation.

Subgroup analyses by baseline rickets severity (RSS total score ≤ 2.5 versus > 2.5) and age (< five years versus ≥ five years) were conducted in the CL301 study; subgroup analyses by baseline rickets severity (RSS total score < 1.5 versus ≥ 1.5) were conducted in the CL201 study; and subgroup analyses by baseline BPI average pain (> 6.0 or ≤ 6.0) were conducted in the CL303 study. To compare treatment effects in subgroups in any study, a test of interaction should be conducted. If the result of the interaction test is not significant, then there is no observable subgroup effect; however, such analysis was not reported by the sponsor.

In studies CL301, CL201, and CL205, the normal range of serum phosphorus used was 1.03 mmol/L to 1.97 mmol/L. No reference was provided for this range. The clinical experts consulted for this review indicated that they used the numbers provided in the CALIPER Database,[9] which provides biochemical markers across the pediatric age span (birth to 18 years). This database indicates that the normal range of serum phosphorus for the age group of one year to less than five years of age is higher than the range for the age group of five years to less than 13 years of age. In addition, none of the measures reported in the CALIPER Reference Interval Database[9] had the lower bound for the age group of one year to less than five years at 1.03 (the lowest reported is 1.26 mmol/L). The sponsor clarified that the serum phosphorus levels were determined according to the standards in place in local laboratories. However, the normal range of serum phosphorus used was the same regardless of age; as a result, there is uncertainty about the number of patients younger than five years of age who actually achieved the normal range of serum phosphorus.

The outcome measures used in the studies, including RSS scores, were demonstrated to have relatively high inter-rater reliability and validity. However, the small differences in PROs, for example — in either within-group change from baseline or between the comparison arms — would still make it difficult to judge whether such differences were attributable to the study drug or to random variation. Also, an MCID in the XLH population is

not available for any of these outcomes. Overall, the included studies consistently showed a beneficial effect in favour of burosumab compared to the selected active comparator or placebo, both in children and adults.

External Validity

Patients enrolled in the studies appear to be similar, in general, to patients with XLH in Canada.

In Study CL301, a considerable proportion of patients (50%) were screened in the studies, but did not enter the treatment phase. The most common reason given was RSS total score of less than 2 (55 patients); this may significantly compromise the generalizability of the results to patients with mild rickets severity as measured by an RSS total score of less than 2. Moreover, all the included studies recruited patients with highly selective criteria. For example, patients with unfavourable renal function were excluded. This restriction would have made the results of the risk-benefit profile from the studies less representative than it would be for patients not included in the studies.

The starting dose of burosumab used in Study CL201 was not approved by Health Canada.

There was lack of information about the use of burosumab in the adolescent population, as no clinical trials in the burosumab development program enrolled patients aged 13 years to 17 years. The indication was extended to this age group by Health Canada based on pharmacokinetic and pharmacodynamic models as well as the efficacy and safety data submitted for children from one year to 12 years of age along with adult patients.

XLH is a lifelong disease. However, in both adults and children, there were limited data on long-term use of burosumab. Furthermore, it is unclear whether the duration of the treatment period in the included trials allowed sufficient time to adequately assess mobility, pain, fatigue, and HRQoL outcomes.

In Study CL303, patients in the placebo arm did not receive any active or supportive treatment; however, in clinical practice, symptomatic patients might receive conventional therapy of oral phosphate supplements and active vitamin D analogues. Hence, Study CL303 was biased in favour of the burosumab treatment group, especially for the primary outcome (proportion of patients achieving mean serum phosphorus levels above the LLN), given that patients in the placebo treatment group did not receive oral phosphate supplements, and patients had to have serum phosphorus levels lower than the LLN (0.81 mmol/L) to be eligible to enrol in the study. Thus, the findings of the study may not reflect the comparative effectiveness to be achieved in the real-world setting.

Indirect Evidence

No indirect evidence was submitted by the sponsor or identified in our literature search that would match the inclusion and exclusion criteria of this review.

Other Relevant Studies

Single-Arm Study CL304

In addition to CL303, the sponsor submitted another study evaluating the effects of burosumab on the improvement of osteomalacia in adult patients with XLH. Details of the study characteristics are provided in Table 17.

Table 17: Details of Study CL304

		Study CL304
Designs and Populations	**Study design**	Phase III, OL, multi-centre study
	Locations	6 centres in the US, Japan, and France
	Randomized (N)	Not an RCT
	Inclusion criteria	• Patients aged 18 years to 65 years and diagnosed with XLH • Serum phosphorus < 0.81 mmol/L and TmP/GFR < 2.5 mg/dL at screening • Skeletal pain attributed to XLH or osteomalacia, BPI-Q3 score ≥ 4 at screening • eGFR ≥ 60 mL/min or eGFR 45 mL/min to < 60 mL/min at screening, with confirmation that renal insufficiency was not due to nephrocalcinosis • Females of child-bearing potential must have had a negative urine pregnancy test at baseline and be willing to have additional pregnancy tests during the study
	Exclusion criteria	• Treatment with oral phosphate, vitamin D therapy, or bisphosphonates < 2 years prior to screening • Prior to screening: aluminum hydroxide antacids, acetazolamides, and thiazides < 7 days; denosumab < 6 months; teriparatide < 2 months; chronic use of systemic corticosteroids (> 10 days in the 2 months prior to screening) • Evidence of hyperparathyroidism at screening (corrected serum calcium level ≥ 10.8 mg/dL, serum iPTH ≥ 2.5 times ULN at screening, and/or use of medication to suppress PTH < 60 days before screening) • PT/PTT outside normal range at screening • Evidence of any disease or use of anticoagulant medication that may increase the risk of bleeding during the biopsy procedure • Documented dependence on narcotics • Use of burosumab or any other therapeutic monoclonal antibody < 90 days prior to screening • Presence or history of any hypersensitivity, allergic, or anaphylactic reactions to any monoclonal antibody or burosumab excipients that placed the patient at increased risk for AEs • History of allergic reaction to or AEs with tetracycline or demeclocycline • History of positive test for HIV antibody, hepatitis B surface antigen, and/or hepatitis C antibody • History of recurrent infection, predisposition to infection, or known immunodeficiency • Presence of malignant neoplasm (except basal cell carcinoma) • Presence or history of any condition that placed the patient at high risk of poor treatment compliance or of not completing the study
Drugs	**Intervention**	Burosumab 1 mg/kg SC injections q.4.w.
	Comparator(s)	No
Duration	**Phase**	
	Run-in	No
	OL treatment	48 weeks
	Follow-up	After completion of the OL treatment, patients continued into an additional 48-week treatment extension period.
Outcomes	**Primary end point**	Improvement in osteoid volume/bone volume obtained from baseline to week 48
	Secondary and exploratory end points	Patient-reported outcomes (e.g., BPI, BFI) Serum phosphorus Markers of bone turnover Fracture and/or pseudofracture healing

		Study CL304
		Safety
NOTES	**Publications**	Insogna et al. 2019 (manuscript)[64]

AE = adverse event; BFI = Brief Fatigue Inventory; BPI = Brief Pain Inventory; BPI-Q3 = Brief Pain Inventory – Question 3; eGFR = estimated glomerular filtration rate; iPTH = intact parathyroid hormone; OL = open-label; PTH = parathyroid hormone; PT/PTT = prothrombin time/partial thromboplastin time; q.4.w. = every 4 weeks; RCT = randomized controlled trial; SC = subcutaneous; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; ULN = upper limit of normal; XLH = X-linked hypophosphatemia.

Source: Clinical Study Report for Study CL304.[65]

Description of Studies

Study CL304 (N = 14) was a phase III, open-label, single-arm, ongoing study designed to assess the effectiveness and safety of burosumab treatment on bone quality and osteomalacia associated with XLH for adult patients.[65]

After screening, eligible participants were provided tetracycline or demeclocycline. A bone biopsy was performed five days after the last dosing day for tetracycline or demeclocycline. Iliac crest bone biopsies were performed at baseline, and baseline histologic and histomorphometric assessments of the bone biopsy specimens were performed to assess sample quality and confirm the presence of osteomalacia in at least eight patients. If a patient was determined not to have osteomalacia at the initial biopsy, that patient continued in the study but did not undergo the second bone biopsy at week 48. All eligible patients received burosumab 1 mg/kg for 48 weeks during the treatment period. After completion of the open-label treatment period, patients continued into an additional 48-week treatment extension period until week 96. For patients who completed the 48-week, open-label treatment and chose not to enrol in the planned extension study, and patients who discontinued the study early, a safety follow-up phone call was made 12 weeks after the final dose of the that treatment period to collect information on any ongoing or new AEs, SAEs, and concomitant medications. The phone call was not required for patients who entered the extension study.

Post-baseline radiographs were compared with baseline radiographs by a trained central reader who was blinded to patient data.

Populations

Inclusion and Exclusion Criteria

The study was conducted in adults with a confirmed diagnosis of XLH. Each patient's skeletal pain was required to be attributed to XLH and associated osteomalacia. The key exclusion criteria included: receiving oral phosphate and active vitamin D therapy in the two years prior to enrolment; evidence of hyperparathyroidism at screening; abnormal or partial thromboplastin time; evidence of any disease or use of anticoagulants that could increase the risk of bleeding during the biopsy procedure; use of burosumab or any other therapeutic monoclonal antibody within 90 days prior to screening; history of recurrent infection or predisposition to infection; known immunodeficiency; or presence or history of any condition that placed the patient at high risk of poor treatment compliance or of not completing the study.

Baseline Characteristics

Fourteen patients were enrolled in Study CL304. At baseline, patients' mean age was 40 years. The majority were female (57%) and white (64%). The average time since XLH diagnosis was 32 years. Most had a history of osteoarthritis (57%), had undergone orthopedic surgeries (79%), or had dental and/or oral conditions (93%). Most received phosphate supplement and vitamin D therapy (86%). All patients had bowing in extremities and enthesopathy. Four patients had active pseudofractures at baseline. Evaluable biopsies were available for 11 patients; the mean OV/BV was 26.1%.

Details of patients' baseline characteristics are provided in Table 18.

Table 18: Summary of Baseline Characteristics in Study CL304 – FAS

Baseline characteristics	Study CL304 Burosumab 1 mg/kg (N = 14)
Age, years, mean (SD)	40.1 (8.7)
Sex, n (%)	
Male	6 (42.9)
Female	8 (57.1)
Race, n (%)	
Asian	4 (28.6)
Black or African-American	1 (7.1)
White	9 (64.3)
Weight, kg, mean (SD)	70.26 (22.00)
Height, cm, mean (SD)	150.42 (8.98)
BMI, kg/m^2, mean (SD)	30.80 (8.47)
Time since XLH diagnosis, years, mean (SD)	32.02 (15.08)
History of osteoarthritis, n (%)	8 (57.1)
Experienced renal conditions, n (%)	1 (7.1)
History of dental/oral conditions, n (%)	13 (92.9)
History of orthopedic surgeries, n (%)	11 (78.6)
Prior conventional therapy, n (%)	
Phosphate only	0
Vitamin D only	1 (7.1)
Phosphate + vitamin D	12 (85.7)
No phosphate/vitamin D	1 (7.1)
Phosphate years, mean (SD)	13.25 (6.72)
Vitamin D years, mean (SD)	14.77 (5.05)
Baseline key phosphate metabolism parameters (FAS)	
Serum phosphorus, mg/dL, mean (SD)	2.24 (0.40)
Serum 1,25(OH)$_2$D, pg/mL, mean (SD)	37.25 (11.69)
Baseline histomorphometry parameters (PAS[a])	
Osteoid volume/bone volume, %, mean (SD)	26.12 (12.36) (reference: 1.85 [1.07])[b]
Osteoid thickness, µm, mean (SD)	17.21 (4.11) (reference: 9.27 [2.10])[b]

Baseline characteristics	Study CL304 Burosumab 1 mg/kg (N = 14)
Baseline radiographic characteristics (FAS)	
Patients with bowing in any extremity, n (%)	14 (100)
Patients with enthesopathy, n (%)	14 (100)
Patients with active fractures, n (%)	0
Patients with healed fractures, n (%)	6 (42.9)
Patients with active pseudofractures, n (%)	4 (28.6)
Patients with healed pseudofractures, n (%)	5 (35.7)
Patients presented with osteomalacia, n (%) OV/BV, % (SD)	11 (78.6) 26.1 (12.4)

BMI = body mass index; FAS = full analysis set; OV/BV = osteoid volume/bone volume; PAS = primary analysis set; SD = standard deviation; XLH = X-linked hypophosphatemia.

[a] PAS included 11 patients who had evaluable bone biopsies at baseline.

[b] Reference values were obtained from healthy post-menopausal women.

Source: Clinical Study Report for Study CL304.[65]

Interventions

After screening, all eligible patients received SC burosumab 1 mg/kg (rounded to the nearest 10 mg) every four weeks for 48 weeks during the open-label treatment period. The amount of drug administered was calculated based on baseline body weight, and the maximum dose was 90 mg. After completion of the open-label treatment period, patients continued into an additional 48-week treatment extension period until week 96.

Outcomes

The primary efficacy end point was the percentage change from baseline in OV/BV at week 48 based on analyses of iliac crest bone biopsies. The other efficacy end points included the proportion of patients achieving mean serum phosphorus levels above the LLN at various time points, phosphate homeostasis, bone metabolism, and percentage change from baseline in additional histomorphometric parameters (e.g., O.Th). Healing of active pseudofractures and/or fractures was reported as well. Patient-reported outcomes, such as BPI pain severity and pain interference scores and BFI scores, were measured. Harm outcomes were reported, including AEs, SAEs, WADEs, and AEs of particular interest.

Statistical Analysis

The planned sample size included approximately 14 adult patients with XLH and at least eight patients with a confirmed diagnosis of osteomalacia. In addition, to ensure a level of gender balance, at least three patients of each sex were required. The sponsor indicated that the sample size and study duration were believed to be sufficient to enable characterization of burosumab effects on bone tissue and skeletal health, but did not provide a rationale.

The week 48 primary analysis was conducted after all patients either completed the open-label treatment period or discontinued the study during that period. A week 96 analysis will be conducted after all patients have completed the week 96 assessments or discontinued the study during the treatment extension period. When the sample size and number of observations allowed, the change from baseline over time was analyzed using a GEE model that included time of visit as the categorical variable and adjusted for baseline

measurement. If the number of observations was insufficient for analyses using a GEE model, a t-test was performed for continuous variables, and a 95% CI of the proportion was provided for binary variables. In general, statistical tests were two-sided at the alpha = 0.05 significance level, and two-sided CIs were used. No adjustments for multiplicity were made. Continuous variables were summarized by mean, SD, SE, median, first quartile, third quartile, minimum, and maximum. Categorical variables were summarized by the numbers and percentages of patients.

Analysis Populations

The FAS, used for the analyses of efficacy end points, and the SAS, used for the analyses of all safety end points, included patients who received at least one dose of burosumab during the study. The PAS included patients who had bone biopsy data at baseline and week 48.

Results

Patient Disposition

Among the 25 patients who were screened for the study, 14 were enrolled and received at least one dose of burosumab. There were 13 patients who completed the 48-week, open-label treatment and entered the extension study. One patient discontinued the study before week 48 visit (withdrew consent). At the data cut-off of August 30, 2017, 13 patients remained on the study. At the data cut-off, six patients (42.9%) had major protocol deviations, which could have a significant impact on the conduct of the study, its outcomes, or both.

Details of patient disposition are provided in Table 19.

Table 19: Patient Disposition in Study CL304 – Week 48 Analysis

	Study CL304
	Burosumab 1 mg/kg
Screened, N	25
Patients with ≥ 1 dose, n (%)	14 (56)
Patients who completed week 0 to week 48, n (%)	13 (92.9)
Discontinued during OL week 0 to week 48, n (%)	1 (7.1)
Reason for discontinuation, n (%)	
Patient withdrew consent	1 (7.1)
FAS, n (%)	14 (100)
Patients with major protocol deviation, n (%)	6 (42.9)
PAS, n (%)[a]	11 (78.6)
SAS, n (%)	14 (100)
Treatment extension analysis set, n (%)	13 (92.9)
Patients who discontinued after OL period prior to the cut-off date	0

FAS = full analysis set; OL = open-label; PAS = primary analysis set; SAS = safety analysis set.

[a] Patients with baseline and follow-up (week 48 or end of treatment) bone biopsy data.

Source: Clinical Study Report for Study CL304.[65]

Exposure to Study Treatments

The mean duration of exposure during the 48-week, open-label treatment period was 338 days, indicated that most patients were exposed to the study drug for 48 weeks. Details of exposure to study drug are provided in Table 20.

Table 20: Extent of Exposure in Study CL304 – Safety Analysis Set

	Burosumab 1 mg/kg (N = 14)
Extent of exposure, days	
OL treatment period (week 0 to week 48), mean (SE)	338.0 (0.81)
OL treatment period + extension period (week 0 cut-off), mean (SE)	424.9 (16.28)

OL = open-label; SE = standard error.

Source: Clinical Study Report for Study CL304.[65]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported here.

Patient-Reported Outcomes

There was a statistically and clinically significant (MCID: two-point change) improvement in the BPI worst pain scores from baseline to week 48 (LS mean change: −1.9 [95% CI, −3.17 to −0.55; P = 0.0054]), indicating a reduced intensity of the worst pain from baseline. In addition, the LS mean (SE) change in BPI pain severity scores and BPI pain interference scores were statistically significantly reduced from baseline, indicating an improvement in severity of pain and the impact of pain on daily function in the study population.

At week 48, the LS mean change in BFI worst fatigue scores from baseline was −1.6 (95% CI, −2.82 to −0.30; P = 0.0156), indicating a reduced worst fatigue intensity from baseline. An MCID for the BFI worst fatigue scores was not identified for patients with XLH; therefore, the clinical importance of the improvement in BFI worst fatigue score is unknown. In addition, the LS mean change in BFI global fatigue scores from baseline was −1.2 (95% CI, −2.33 to −0.08; P = 0.0359), indicating an improvement in fatigue in the study population. MCIDs for the BFI worst fatigue and global fatigue scores were not identified for patients with XLH; therefore, the clinical importance of the improvement in these outcomes is unknown.

Details of patient-reported outcomes at week 48 are presented in Table 21.

Table 21: Patient-Reported Outcomes in Study CL304 – Full Analysis Set

	Study CL304
	Burosumab 1 mg/kg (N = 14)
BPI worst pain score, mean (SD)	
Number of patients analyzed, n	13
Baseline	6.64 (1.99)
Week 48	4.92 (2.60)
LS mean change from baseline mean (SE) 95% CI P value	 −1.86 (0.67) −3.17 to −0.55 P = 0.0054
BPI pain severity score, mean (SD)	
Number of patients analyzed, n	13
Baseline	5.09 (1.80)
Week 48	3.42 (2.24)
LS mean change from baseline mean (SE) 95% CI P value	 −1.77 (0.55) −2.84 to −0.69 P = 0.0013
BPI pain interference score, mean (SD)	
Number of patients analyzed, n	13
Baseline	5.22 (2.26)
Week 48	3.96 (2.68)
LS mean change from baseline mean (SE) 95% CI P value	 −1.47 (0.53) −2.51 to −0.42 P = 0.0060
BFI worst fatigue score, mean (SD)	
Number of patients analyzed, n	13
Baseline	6.79 (1.85)
Week 48	5.46 (2.50)
LS mean change from baseline mean (SE) 95% CI P value	 −1.56 (0.65) −2.82 to −0.30 P = 0.0156

	Study CL304 Burosumab 1 mg/kg (N = 14)
BFI global fatigue score, mean (SD)	
Number of patients analyzed, n	13
Baseline	5.01 (2.06)
Week 48	3.99 (2.40)
LS mean change from baseline mean (SE) 95% CI P value	 −1.20 (0.57) −2.33 to −0.08 P = 0.0359

BFI = Brief Fatigue Inventory; BPI = Brief Pain Inventory; CI = confidence interval; FAS = full analysis set; GEE = generalized estimating equation; LS = least squares; SD = standard deviation; SE = standard error.

Note: The GEE estimates were from the GEE model, which included the change from baseline in BPI or BFI end point as the dependent variable, visit as a fixed factor, and baseline of BPI or BFI end point as covariate, with compound symmetry covariance structure.

Source: Clinical Study Report for Study CL304.[65]

Changes in Osteomalacia

In total, 11 patients had osteomalacia as determined by evaluation of the iliac crest bone biopsy at baseline.

At week 48, the mean OV/BV decreased statistically significantly from baseline, with a mean change of −14.9% (SD = 10.97). In addition, O.Th statistically significantly decreased from baseline, with a mean change of −5.65 µm (SD = 2.76).

Details of change in histomorphometric parameters are presented in Table 22.

Table 22: Results of Change for Osteomalacia in Study CL304 – Primary Analysis Set

	Study CL304 Burosumab 1 mg/kg (N = 14)
OV/BV, %, mean (SD)	
Number of patients analyzed, n	10
Baseline	26.12 (12.36)
Week 48	11.85 (6.60)
Change from baseline	−14.94 (10.97)
% change from baseline Mean (SD) 95% CI P value	 −54.18 (20.21) −68.64 to −39.72 P < 0.0001
O.Th, µm, mean (SD)	
Number of patients analyzed, n	11
Baseline	17.21 (4.11)
Week 48	11.55 (3.11)
Change from baseline	−5.65 (2.76)
% change from baseline Mean (SD) 95% CI P value	 −32.21 (11.97) −40.25 to −24.17 P < 0.0001

CI = confidence interval; O.Th = osteoid thickness; OV/BV = osteoid volume/bone volume; PAS = primary analysis set; SD = standard deviation.

Source: Clinical Study Report for Study CL304.[65]

Phosphate Homeostasis

At the end of week 48, the LS mean change from baseline in serum phosphorus concentration was 0.06 mmol/L (SE = 0.025), representing a percentage change of 11% from baseline in the study population. At the midpoint of the dose interval between baseline and week 24, 13 patients (92.9%) achieved mean serum phosphorus levels above the LLN.

At week 48, the LS mean change from baseline in TmP/GFR was 0.20 mg/dL (SE = 0.10), representing a percentage change of 13.12% from baseline in the study population.

At week 48, there was no change from baseline in TRP (mean change = 0).

There were no statistically significant changes observed from baseline for 24-hour urinary phosphorus in either group. The LS mean change from baseline in 24-hour urinary phosphorus was −0.04 g/24h (SE = 0.08), and the percentage change in 24-hour urinary phosphorus was −3.11 g/24h.

In addition, there was no statistically significant change for serum $1,25(OH)_2D$ at the end of week 48.

Details of change in phosphate homeostasis are presented in Table 23.

Table 23: Results of Phosphate Homeostasis in Study CL304 – Full Analysis Set

	Study CL304
	Burosumab 1 mg/kg (N = 14)
Serum phosphorus, mmol/L, mean (SD)	
Number of patients analyzed, n	14
Baseline	0.72 (0.13)
Week 24	0.84 (0.10)
Week 48	0.78 (0.10)
LS mean change from baseline, mean (SE)	0.06 (0.025)
LS mean % change from baseline mean (SE) P value	 11.38 (2.862) P < 0.0001
Percentage achieving mean serum phosphorus levels above LLN at the midpoint of dose interval between baseline and week 24, n (%), 95% CI	
Yes	13 (92.9) (68.5 to 98.7)
TmP/GFR, mg/dL, mean (SD)	
Number of patients analyzed, n	13
Baseline	1.87 (0.31)
Week 48	2.09 (0.36)
LS mean change from baseline, mean (SE)	0.20 (0.10)
LS mean % change from baseline Mean (SE) 95% CI P value	 13.12 (4.29) 4.71 to 21.52 P = 0.0022
TRP, mean (SD)	
Number of patients analyzed, n	13
Baseline	0.84 (0.05)

	Study CL304
	Burosumab 1 mg/kg (N = 14)
Week 48	0.83 (0.08)
LS mean change from baseline, mean (SE)	0 (0.02)
LS mean % change from baseline Mean (SE) 95% CI P value	 −0.13 (2.54) −5.10 to 4.85 P = 0.96
24-hr urinary phosphorus, g/24 hr, mean (SD)	
Number of patients analyzed, n	11
Baseline	0.82 (0.24)
Week 48	0.72 (0.32)
LS mean change from baseline, mean (SE)	−0.04 (0.08)
LS mean % change from baseline Mean (SE) 95% CI P value	 −3.11 (8.66) −20.08 to 13.86 P = 0.72
Serum $1,25(OH)_2D$, pg/mL, mean (SD)	
Number of patients analyzed, n	11
Baseline	37.25 (11.69)
Week 48	33.92 (8.98)
LS mean change from baseline, mean (SE)	−1.72 (4.19)
LS mean % change from baseline Mean (SE) P value	 2.39 (7.39) P = 0.75

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; CI = confidence interval; FAS = full analysis set; GEE = generalized estimating equation; LLN = lower limit of normal; LS = least squares; SD = standard deviation; SE = standard error; TmP/GFR = ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate; TRP = tubular reabsorption of phosphate.

Note: LS mean and P values were based on the GEE model, including the change from baseline and percentage change from baseline for serum phosphorus (or TmP/GFR, TRP, 24-hour urinary phosphorus) as the dependent variable, visit as a fixed factor, and baseline for serum phosphorus (or TmP/GFR, TRP, 24-hour urinary phosphorus) as covariate, with compound symmetry covariance structure.

Source: Clinical Study Report for Study CL304.[65]

Bone Metabolism

At the end of week 48, statistically significant increases from baseline in procollagen type 1 N-propeptide (P1NP) and carboxy terminal cross-linked telopeptide of type 1 collagen (CTx) were observed in the study population. However, there was no statistically significant change for serum BALP at the end of week 48.

Details of change in biomarkers of bone turnover are presented in Table 24.

Table 24: Results of Bone Metabolism – Full Analysis Set

	Study CL304 Burosumab 1 mg/kg (N = 14)
P1NP, ng/mL, mean (SD)	
Number of patients analyzed, n	13
Baseline	77.00 (33.27)
Week 48	127.31 (57.88)
LS mean change from baseline, mean (SE)	52.49 (11.55)
LS mean % change from baseline Mean (SE) P value	 76.86 (14.11) P < 0.0001
CTx, pg/mL, mean (SD)	
Number of patients analyzed, n	13
Baseline	646.93 (401.64)
Week 48	828.69 (420.48)
LS mean change from baseline, mean (SE)	175.13 (44.02)
LS mean % change from baseline Mean (SE) P value	 35.86 (7.40) P < 0.0001
Serum BALP, mcg/L, mean (SD)	
Number of patients analyzed, n	13
Baseline	20.43 (9.29)
Week 48	22.77 (14.97)
LS mean change from baseline, mean (SE)	4.50 (3.99)
LS mean % change from baseline Mean (SE) P value	 24.35 (17.63) P = 0.1672

BALP = bone-specific alkaline phosphatase; CTx = carboxy terminal cross-linked telopeptide of type 1 collagen; GEE = generalized estimating equation; LS = least squares; P1NP = procollagen type 1 N-propeptide; SD = standard deviation; SE = standard error.

Note: LS means and P values were based on the GEE model, including the change from baseline and percentage change from baseline for serum phosphorus as the dependent variable, visit as a fixed factor, and baseline for serum phosphorus as a covariate, with compound symmetry covariance structure.

Source: Clinical Study Report for Study CL304.[65]

Pseudofractures

At baseline, there were four cases of active pseudofractures. At the end of 48-week treatment with burosumab, three of the cases had healed, while data for the fourth patient were missing. There was no report of active fractures at baseline in the study population.

Details of change in pseudofractures are presented in Table 25.

Table 25: Results of Change in Number of Pseudofractures in Study CL304 – Full Analysis Set

	Study CL304
	Burosumab 1 mg/kg (N = 14)
Pseudofracture, n (%)	
Number of patients analyzed, n	14
Number of active pseudofractures at baseline, n	4
Number of pseudofractures at week 48, n (% baseline)	
Healed	3 (75.0)
Missing	1 (25.0)
New findings	0

Source: Clinical Study Report for Study CL304.[65]

Harms

Only those harms identified in the review protocol are reported here.

Adverse Events

Through the data cut-off date of August 30, 2017, all patients in Study CL304 reported at least one AE. The majority of the AEs were grade 1 and grade 2. The most commonly reported AEs included procedural pain (50%), arthralgia (36%), pain (36%), back pain (29%), and muscle spasms (29%).

Serious Adverse Events

Two patients reported SAEs: one paresthesia and one migraine.

Withdrawals Due to Adverse Events

No patients withdrew from the study or discontinued treatment due to AEs.

Mortality

No deaths were reported by the data cut-off date.

Notable Harms

The reported AEs of particular interest included ISRs (36%), hypersensitivity (57%), and restless legs syndrome (14%).

Details of the safety evaluation are presented in Table 26.

Table 26: Summary of Harms in CL304 – Safety Analysis Set

	Study CL304
	Burosumab 1 mg/kg (N = 14)
Patients with ≥ 1 AE	
n (%)	14 (100): • 7 procedural pain (50) • 5 arthralgia (35.7) • 5 pain (35.7) • 4 back pain (28.6) • 4 muscle spasms (28.6) • 4 tooth abscesses (28.6)
Patients with ≥ 1 SAE	
n (%)	2 (14.3)
	• 1 paresthesia • 1 migraine
Patients with ≥ 1 WDAE	
n (%)	0
Deaths	
n (%)	0
Notable harms	
Injection-site reactions, n (%)	5 (35.7)
Hypersensitivity, n (%)	8 (57.1)
Hyperphosphatemia, n (%)	0
Ectopic mineralization, n (%)	0
Restless legs syndrome, n (%)	2 (14.3)

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report for Study CL304.[65]

Critical Appraisal

Internal Validity

Study CL304 was designed to evaluate the effects of burosumab on bone quality and improvement in osteomalacia in adult patients with XLH. All patients received open-label burosumab therapy for 48 weeks. As a rare disease, XLH posed a practical recruitment challenge for clinical trials. The planned sample size in Study CL304 included 14 adult patients with XLH and at least eight with a confirmed diagnosis of osteomalacia. The sponsor indicated that the sample size and study duration were believed to be sufficient to enable characterization of burosumab effects on bone tissue and skeletal health, but did not provide a rationale. An FAS was defined as patients who received at least one dose of burosumab during the study. One patient discontinued the study before the week 48 visit. Sensitivity analysis or subgroup analysis was not performed in this small trial. Therefore, the treatment effect of the study drug among the interested subgroups cannot be fully explored.

Other major limitations of Study CL304 were the open-label study design and lack of randomization and comparators. The open-label study design and within-group comparisons to baseline in the trials may have had an impact on the subjective, patient-

reported questionnaires on pain, fatigue, and physical function, such as the BPI, BFI, or WOMAC. Furthermore, the absence of a comparator group makes it challenging to interpret small changes from baseline. In Study CL304, the primary outcome measure was change in OV/BV at the study end point. Decrease in OV/BV from baseline indicates improvement in osteomalacia. Although an MCID for change in OV/BV in the study population was not identified, reductions in osteoid volume and thickness are essential for healing of osteomalacia, which is in turn required for preventing and healing pseudofractures and fractures. Therefore, reduction in OV/BV can translate to important clinical benefits, such as relief in skeletal pain, prevention of pseudofracture or fracture, or improvement in HRQoL. However, the extent to which this is possible is uncertain.

External Validity

The study included a small number of patients. Given the small sample size and the fact that no Canadian study site was included, it is unclear whether the results can be generalized to the Canadian patient population. The clinical experts consulted for this review acknowledged the difficulties involved in recruiting patients for the invasive bone biopsy, and indicated that it would be even more challenging to recruit patients who would undergo a second bone biopsy 48 weeks from baseline. The dose of burosumab 1 mg/kg every four weeks in Study CL304 was approved by Health Canada.

Discussion

One open-label, single-arm study called CL304 submitted by the manufacture is included in this systematic review. The study included adult patients with XLH and associated osteomalacia, which was confirmed by bone biopsy at screening. All eligible patients received burosumab 1 mg/kg for 48 weeks during the treatment. In total, 14 patients were enrolled in this study, 11 of whom had osteomalacia at baseline. After completing the first 48-week treatment, patients were allowed to enter an additional 48-week extension period. The primary outcome measure in this study was the change from baseline in OV/BV at week 48.

The results of Study CL304 showed that treatment with burosumab every four weeks for 48 weeks was associated with statistically significantly reduced OV/BV (mean change: 14.9%; SD = 11.0%) and osteoid thickness (mean change: –5.65 µm; SD = 2.76 µm). The clinical experts indicated that given that three out of four patients with pseudofractures healed during treatment with burosumab, it is likely that the healing can be attributed to the decrease in osteoid. Compared to baseline, treatment with burosumab was also associated with decreased pain intensity and reduced impact of pain on daily function; decreased fatigue intensity and reduced impact of fatigue on daily function; statistically significantly reduced serum phosphorus levels (LS mean change: 0.17 mg/dL; SE = 0.08 mg/dL); and more favourable bone metabolism (increased P1NP level and CTx, but no change in serum $1,25(OH)_2D$). It is unknown if the improvements in these patient-reported outcomes or biomarkers are considered clinically important, as the magnitude of change in most of them was small. Three out of four active pseudofractures at baseline were healed at the end of week 48. All patients reported at least one AE during the treatment, although the majority of the AEs were mild to moderate in severity. There were no unexpected safety signals in the study population.

The major limitations of Study CL304 are small sample size, the open-label study design, and the lack of randomization and comparators. The study results should be interpreted

with caution, given the significant uncertainty. The generalizability of the study results to the Canadian patient population is unclear.

Conclusions

The results of a single-arm, open-label study (Study CL304) including 14 patients suggested that 48-week treatment with burosumab was associated with improvements in osteomalacia, patient-reported pain and fatigue, serum phosphorus levels, and bone metabolism biomarkers in adult patients with XLH. Three out of four pseudofractures at baseline were healed at the end of 48-week treatment. All patients experienced AEs, although the majority were mild to moderate in severity. There were no unexpected safety signals in the study population. Due to the uncontrolled study design and high degree of uncertainty related to the small sample size, the study results should be interpreted with caution.

Long-term Extension Studies

Study CL201 Extension, up to Week 160

Study CL201 was a randomized, open-label, phase II study evaluating the pharmacodynamic, efficacy, and safety of burosumab in 52 children aged five years to 12 years old with XLH.[66] This study comprised a 16-week individual dose titration period, a 48-week treatment period, a 96-week extension period I (week 64 to week 160) and a 56-week extension period II (week 160 to week 216). Patients who completed the initial 48-week open-label treatment with two burosumab treatment regimens (every two weeks and every four weeks) could enter the extension periods. The goal of extension period I was to evaluate the long-term safety and efficacy of burosumab. All patients received burosumab every two weeks during the extension periods. After week 160, patients could choose to continue burosumab treatment up to 56 weeks (extension period II). The goal of extension period II was to continue to provide burosumab treatment to patients until the availability of a separate rollover study or through September 2018 while continuing to collect long-term safety and efficacy data. The results of extension period I (up to week 160) are presented in this review.

Methods

After completion of the 48-week, open-label burosumab treatment period, patients who were initially randomized to the every-two-weeks and every-four-weeks regimens were allowed to enter extension period I. All patients received burosumab every two weeks during this period. Changes in the severity of rickets were assessed by central readings using the RSS and RGI-C scoring systems.

Interventions

All patients received open-label burosumab every two weeks during the extension periods. Patients who received the burosumab every-two-weeks regimen during the initial 48-week treatment period continued to receive the same dose at the same dose interval (referred to as the every-two-week group). For patients originally assigned to the every-four-weeks regimen, their regimen of burosumab in the extension period was initiated at week 64, using 60% of the most recent monthly dose every two weeks (referred to as the every-four-weeks-followed-by-every-two-weeks group). Therefore, the total dose was approximately 20% higher per month compared with the patients' every-four-weeks dose. In the transition to the every-two-weeks regimen, the every-two-weeks dose was titrated when needed,

during the first three months of the extension, to maintain a serum phosphorus level at or above the patient's week 64 level.

Outcomes

By the end of extension period I (week 160), efficacy outcomes related to radiographic changes, phosphate homeostasis, bone metabolism, and mobility were evaluated. Change from baseline in severity of rickets as measured by RSS total score was the primary efficacy end point in Study CL201. A single, central, independent rater performed all RSS ratings for all radiographs for the study. Patient-reported outcomes, such as POSNA-PODCI scale scores and SF-10 scores, were measured. Harm outcomes were reported at week 160 as well, including AEs, SAEs, WADEs, and AEs of particular interest.

Statistical Analysis

Week 160 analysis was conducted after all patients had completed week 160. Continuous variables were summarized with means, SD, SE, medians, first quartile, third quartile, minimums, and maximums. Categorical variables were summarized by counts and by percentages of patients in corresponding categories. A GEE approach was used to assess the change over time in repeated measures (e.g., clinical outcomes). The model included regimen group, study visit, and interaction between regimen and study visit as categorical variables.

No imputation of missing data was made in general. Missing data were treated as missing and excluded from the analysis. No adjustment for multiplicity was made.

In Study CL201, the ITT set consisted of all patients who had received at least one dose of the study drug and had at least one post-dose measurement. The SAS consisted of all patients who received at least one dose of therapy. The pharmacokinetic and pharmacodynamic analysis set consisted of all patients who received at least one dose of therapy and had evaluable serum data.

Patient Disposition

All 52 patients completed 160 weeks of treatment with burosumab. The ITT, SAS, and pharmacokinetic and pharmacodynamic analysis sets were the same; each comprised all 52 patients.

Exposure to Study Treatments

During extension period I, the mean burosumab dose per administration was 1.05 mg/kg (0.97 mg/kg in the every-two-weeks group and 1.14 mg/kg in the every-four-weeks-followed-by-every-two-weeks group), based on data from 40 patients.

Efficacy

At week 160, 41 patients were evaluable for analysis of RSS. Statistically significant reductions from baseline in RSS total score, RSS wrist score, and RSS knee score were observed in patients receiving burosumab every two weeks in the extension period. The LS mean changes were −0.91 (95% CI, −1.08 to −0.73), −0.23 (95% CI, −0.31 to −0.15), and −0.66 (95% CI, −0.80 to −0.52) for the total score, wrist score, and knee score, respectively. An RSS responder was defined a patient who experienced a reduction in RSS total score from baseline of at least 1.0 point. Overall, the percentage of RSS responders was 58.6% at week 160.

At week 160, the RGI-C global score (mean = 1.89), RGI-C wrist score (mean = 1.80), and RGI-C knee score (mean = 1.93) were all positive, indicating substantial healing of rickets.

However, MCIDs for the RSS and RGI-C were not identified for patients with XLH. Therefore, the clinical importance of the improvement in these outcomes is unknown.

Details of radiographic changes associated with burosumab therapy in the study population are presented in Table 27.

Table 27: Results of Radiographic Responses in Study CL201 – Intention-to-Treat Set

	Study CL201		
	q.2.w. (N = 26)	q.4.w. → q.2.w. (N = 26)[a]	Overall (N = 52)
RSS total score, mean (SD)			
Number of patients analyzed, n	19	22	41
Baseline	1.92 (1.17)	1.67 (1.00)	1.80 (1.09)
Week 64	0.81 (0.60)	0.94 (0.52)	0.88 (0.56)
Week 160	0.89 (0.59)	0.95 (0.60)	0.93 (0.59)
LS mean change from baseline to week 160 Mean (95% CI) P value	−0.98 (−1.23 to −0.73) P < 0.0001	−0.83 (−1.07 to −0.60) P < 0.0001	−0.91 (−1.08 to −0.73) P < 0.0001
RSS wrist scores, mean (SD)			
Number of patients analyzed, n	19	21	40
Baseline	0.71 (0.62)	0.48 (0.52)	0.60 (0.58)
Week 64	0.31 (0.32)	0.35 (0.28)	0.33 (0.30)
Week 160	0.37 (0.33)	0.38 (0.22)	0.38 (0.28)
LS mean change from baseline to week 160 Mean (95% CI) P value	−0.27 (−0.40 to −0.14) P < 0.0001	−0.20 (−0.29 to −0.10) P < 0.0001	−0.23 (−0.31 to −0.15) P < 0.0001
RSS knee scores, mean (SD)			
Number of patients analyzed, n	19	22	41
Baseline	1.21 (0.68)	1.19 (0.60)	1.20 (0.64)
Week 64	0.50 (0.47)	0.60 (0.38)	0.55 (0.42)
Week 160	0.53 (0.49)	0.59 (0.45)	0.56 (0.46)
LS mean change from baseline to week 160 Mean (95% CI) P value	−0.70 (−0.91 to −0.50) P < 0.0001	−0.62 (−0.80 to −0.43) P < 0.0001	−0.66 (−0.80 to −0.52) P < 0.0001
RSS responder, n/N (%)			
Week 64	16/20 (80.0)	12/19 (63.2)	28/39 (71.8)
Week 160	8/14 (57.1)	9/15 (60.0)	17/29 (58.6)
RGI-C global scores, mean (95% CI)			
Number of patients analyzed, n	26	25	51

	Study CL201		
	q.2.w. (N = 26)	q.4.w. → q.2.w. (N = 26)[a]	Overall (N = 52)
Week 64	1.56 (1.34 to 1.78)	1.58 (1.36 to 1.80)	1.57 (1.41 to 1.72)
Week 160	1.92 (1.70 to 2.14)	1.86 (1.63 to 2.10)	1.89 (1.73 to 2.05)
P value	P < 0.0001	P < 0.0001	P < 0.0001
RGI-C knee scores, LS mean (95% CI)			
Number of patients analyzed, n	26	26	52
Week 64	1.57 (1.37 to 1.77)	1.53 (1.34 to 1.73)	1.55 (1.41 to 1.69)
Week 160	2.01 (1.80 to 2.21)	1.85 (1.62 to 2.08)	1.93 (1.77 to 2.09)
P value	P < 0.0001	P < 0.0001	P < 0.0001
RGI-C wrist scores, mean (95% CI)			
Number of patients analyzed, n	26	25	51
Week 64	1.65 (1.35 to 1.95)	1.54 (1.29 to 1.78)	1.59 (1.40 to 1.79)
Week 160	1.78 (1.52 to 2.04)	1.83 (1.57 to 2.09)	1.80 (1.62 to 1.99)
P value	P < 0.0001	P < 0.0001	P < 0.0001

CI = confidence interval; GEE = global estimating equation; LS = least squares; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.4.w. → q.2.w. = every 4 weeks, then every 2 weeks; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SD = standard deviation.

[a] Patients in the q.4.w. group were to switch to the q.2.w. group beginning with week 64 dosing.

Note: The GEE model included the change from baseline in RSS (or RGI-C) as the dependent variable, visit, regimen, and visit by regimen as factors, and RSS at baseline as covariate, with exchangeable covariance structure.

Source: Clinical Study Report for Study CL201.[66]

Mobility Measurement – 6-Minute Walk Test

At week 160, a statistically significantly increase from baseline in distance walked within six minutes was observed for both groups: 57.4 m (95% CI, 38.1 to 76.6) in the every-two-weeks group and 56.1 m (95% CI, 32.6 to 79.6) in the every-four-weeks-followed-by-every-two-weeks group. The improvement in 6MWT was considered clinically meaningful, given the MCID of 31 m for the pediatric population.

Details of change in walk distance in the study population are presented in Table 28.

Table 28: Results of Mobility in Study CL201 – Intention-to-Treat Set

	Study CL201		
	q.2.w. (N = 26)	q.4.w. → q.2.w. (N = 26)[a]	Overall (N = 52)
6MWT distance, m, mean (SD)			
Number of patients analyzed, n	26	26	52
Baseline	479.92 (84.80)	486.35 (108.55)	483.13 (96.50)
Week 64	533.85 (58.70)	525.85 (89.53)	529.85 (75.06)
Week 160	538.65 (48.06)	541.00 (78.24)	539.83 (64.30)
LS mean change from baseline to week 160 mean (95% CI) P value	57.38 (38.14 to 76.61) P < 0.0001	56.08 (32.57 to 79.58) P < 0.0001	56.73 (41.55 to 71.90) P < 0.0001

6MWT = 6-minute walk test; CI = confidence interval; GEE = global estimating equation; LS = least squares; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.4.w. → q.2.w. = every 4 weeks, then every 2 weeks; SD = standard deviation.

[a] Patients in the q.4.w. group were to switch to the q.2.w group beginning with week 64 dosing.

Note: The GEE model included change in 6MWT score as the dependent variable; visit, regimen, visit by regimen as factors; and 6MWT at baseline as covariate, with exchangeable covariance structure.

Source: Clinical Study Report for Study CL201.[66]

Patient-Reported Outcome Measures

At week 160, the LS mean changes in overall scale scores from baseline were 13.18 (95% CI 10.48 to 15.89) and 12.72 (95% CI 9.69 to 15.75) for the scales of sports and physical functioning and pain and comfort, respectively, indicating improved functional ability and decreased pain. Details of change in the POSNA-PODCI sports and physical functioning scale and the pain and comfort scale are presented in Table 29. Due to a lack of MCID for POSNA-PODCI, the clinical importance of the improvement in this outcome is unknown.

Table 29: Results of Functional Disability and Pain in Study CL201 – Intention-to-Treat Set

	Study CL201		
	q.2.w. (N = 26)	q.4.w. → q.2.w. (N = 26)[a]	Overall (N = 52)
POSNA-PODCI sports and physical functioning scale, mean (SD)			
Number of patients analyzed, n	25	25	50
Baseline	34.6 (15.7)	32.2 (19.29)	33.4 (17.42)
Week 64	41.7 (15.67)	42.8 (13.67)	42.2 (14.59)
Week 160	47.6 (8.71)	47.5 (9.00)	47.6 (8.77)
LS mean change from baseline to week 160 mean (95% CI) P value	12.04 (7.92 to 16.16) P < 0.0001	14.33 (10.73 to 17.92) P < 0.0001	13.18 (10.48 to 15.89) P < 0.0001
POSNA-PODCI pain and comfort scale, mean (SD)			
Number of patients analyzed, n	26	25	51

	Study CL201		
	q.2.w. (N = 26)	q.4.w. → q.2.w. (N = 26)[a]	Overall (N = 52)
Baseline	35.2 (15.26)	34.8 (16.76)	35.0 (15.85)
Week 64	41.0 (17.04)	43.0 (11.54)	42.0 (14.49)
Week 160	48.8 (12.75)	48.3 (11.53)	48.6 (12.04)
LS mean change from baseline to week 160 Mean (95% CI) P value	 13.06 (8.77 to 17.35) P < 0.0001	 12.38 (7.94 to 16.82) P < 0.0001	 12.72 (9.69 to 15.75) P < 0.0001

CI = confidence interval; GEE = generalized estimating equation; LS = least squares; PODCI = Pediatric Outcomes Data Collection Instrument; POSNA = Pediatric Orthopaedic Society of North America; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.4.w. → q.2.w. = every 4 weeks, then every 2 weeks; SD = standard deviation.

[a] Patients in the q.4.w. group were to switch to the q.2.w. group beginning with week 64 dosing.

Note: The GEE model included change in POSNA-PODCI scale score as the dependent variable; visit, regimen, and visit by regimen as factors; and POSNA-PODCI scale score at baseline as covariate, with exchangeable covariance structure.

Source: Clinical Study Report for Study CL201.[66]

Short Form (10) Health Survey for Children

At week 160, the mean change from baseline in the PHS of the SF-10 was 8.76 (SE = 2.74) in the every-two-weeks group and 5.27 (SE = 2.79) in the every-four-weeks-followed-by-every-two-weeks group. The mean change from baseline in the PSS was 2.13 (SE = 1.91) in the every-two-weeks group and 2.00 (SE = 1.55) in the every-four-weeks-followed-by-every-two-weeks group. The results suggested an improvement in physical and psychosocial HRQoL from baseline in the study population. However, an MCID for the SF-10 was not identified for patients with XLH. Therefore, the clinical importance of the improvement in these outcomes is unknown.

Details of the SF-10 summary scores are provided in Table 30.

Table 30: Results of HRQoL (SF-10) in Study CL201 – Intention-to-Treat Set

	Study CL201		
	q.2.w. (N = 26)	q.4.w. → q.2.w. (N = 26)[a]	Overall (N = 52)
PHS, mean (SD)			
Number of patients analyzed, n	26	25	51
Baseline	41.57 (12.14)	43.21 (10.67)	42.36 (11.37)
Week 64	47.41 (10.43)	47.84 (10.66)	47.61 (10.43)
Week 160	50.33 (9.79)	48.83 (12.15)	49.60 (10.92)
Mean change from baseline to week 160, mean (SE)	8.76 (2.74)	5.27 (2.79)	7.09 (1.95)
PSS, mean (SD)			
Number of patients analyzed, n	26	26	52
Baseline	53.37 (9.52)	52.44 (7.73)	52.92 (8.61)
Week 64	52.85 (8.47)	54.87 (8.07)	53.84 (8.26)
Week 160	55.49 (7.28)	54.64 (6.13)	55.07 (6.68)
Mean change from baseline to week 160, mean (SE)	2.13 (1.91)	2.00 (1.55)	2.06 (1.22)

HRQoL = health-related quality of life; PHS = physical summary scores; PSS = psychosocial summary scores; q.2.w. = every 2 weeks; q.4.w. → q.2.w. = every 4 weeks, then every 2 weeks; q.4.w. = every 4 weeks; q.4.w. → q.2.w. = every 4 weeks, then every 2 weeks; SD = standard deviation; SE = standard error; SF-10 = Short Form (10) Health Survey for Children.

[a] Patients in the q.4.w. group were to switch to the q.2.w. group beginning with week 64 dosing.

Source: Clinical Study Report for Study CL201.[66]

Phosphate Homeostasis

At week 160, the serum phosphorus level statistically significant increased from baseline. The mean change was 0.33 (SD = 0.116) mmol/L. In addition, 36 patients (69.2%) reached the normal range of 1.03 mmol/L to 1.97 mmol/L at week 160. Among them, 19 (73.1%) were in the every-two-weeks group and 17 (65.4%) were in the every-four-weeks-followed-by-every-two-weeks group.

Similarly, statistically significant increases from baseline in TmP/GFR and TRP were observed at week 160.

Details of phosphate homeostasis up to week 160 are presented in Table 31.

Table 31: Results of Phosphate Homeostasis in Study CL201 – PD Analysis Set

	Study CL201		
	q.2.w. (N = 26)	q.4.w. → q.2.w. (N = 26)[a]	Overall (N = 52)
Serum phosphorus, mmol/L, mean (SD)			
Number of patients analyzed, n	26	26	52
Baseline	0.77 (0.131)	0.74 (0.097)	0.75 (0.115)
Week 64	1.08 (0.144)	0.95 (0.103)	1.02 (0.140)
Week 160	1.08 (0.120)	1.08 (0.131)	1.08 (0.125)
Mean change from baseline at week 160 P value	0.31 (0.109) P < 0.0001	0.35 (0.122) P < 0.0001	0.33 (0.116) P < 0.0001

	Study CL201		
	q.2.w. (N = 26)	q.4.w. → q.2.w. (N = 26)[a]	Overall (N = 52)
Number of patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 160, n (%)			
Yes	19 (73.1)	17 (65.4)	36 (69.2)
TmP/GFR, mg/dL, mean (SD)			
Number of patients analyzed, n	24	25	49
Baseline	2.18 (0.49)	1.98 (0.35)	2.08 (0.43)
Week 64	3.35 (0.53)	2.95 (0.46)	3.15 (0.54)
Week 160	3.47 (0.55)	3.43 (0.59)	3.45 (0.56)
Mean change from baseline at week 160 P value	1.24 (0.55) P < 0.0001	1.45 (0.65) P < 0.0001	1.34 (0.61) P < 0.0001
% change from baseline at week 160	61.14 (33.12)	76.91 (39.97)	69.19 (37.24)
TRP, mean (SD)[b]			
Number of patients analyzed, n			
Baseline	0.86 (0.07)	0.84 (0.07)	0.85 (0.07)
Week 64	0.91 (0.02)	0.89 (0.06)	0.90 (0.05)
Week 160	0.91 (0.02)	0.91 (0.03)	0.91 (0.03)
Mean change from baseline at week 160 P value	0.05 (0.07) P value NR	0.07 (0.08) P value NR	0.06 (0.08) P value NR
% change from baseline at week 160	6.64 (9.15)	9.12 (12.83)	7.91 (11.13)
Serum $1,25(OH)_2D$, pg/mL, mean (SD)[c]			
Number of patients analyzed, n	26	26	52
Baseline	41.28 (21.97)	41.37 (15.29)	41.33 (18.74)
Week 64	64.87 (16.36)	53.83 (12.23)	59.57 (15.42)
Week 160	58.32 (16.51)	61.00 (19.74)	59.66 (18.07)
Mean change from baseline to week 160 P value	17.03 (24.89) P = 0.0018	19.64 (22.86) P = 0.0002	18.34 (23.70) P < 0.0001
% change from baseline to week 160	75.32 (84.34)	82.83 (136.96)	79.08 (112.68)

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; NR = not reported; PD = pharmacodynamic; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.4.w. → q.2.w. = every 4 weeks, then every 2 weeks; SD = standard deviation; TmP/GFR = ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate; TRP = tubular reabsorption of phosphate.

[a] Patients in the q.4.w. group were to switch to the q.2.w. group beginning with week 64 dosing.

[b] TRP data were analyzed using the safety analysis set.

[c] $1,25(OH)_2D$ data were analyzed using the pharmacokinetic and pharmacodynamic analysis set.

Note: P values for change from baseline were calculated using the one-sample t-test.

Source: Clinical Study Report for Study CL201.[66]

Bone Metabolism

No data for week 160 are available for biomarkers of bone turnover.

Harms

By week 160, all patients in Study CL201 reported at least one AE. All AEs except for two were mild or moderate in severity. The most commonly reported AEs included headache (75%), cough (69%), vomiting (56%), arthralgia (54%), nasopharyngitis (54%), pain in extremity (52%), ISR (50%), oropharyngeal pain (50%), pyrexia (48%), upper respiratory tract infection (48%), injection-site erythema (44%), and rhinorrhea (42%).

One patient (3.8%) in the every-four-weeks-followed-by-every-two-weeks group reported SAEs. There were no patients who withdrew from the study or from treatment due to AEs. No deaths were reported by week 160.

The AEs of particular interest included ISRs, hypersensitivity, and ectopic mineralization.

Details of the safety evaluation are presented in Table 32.

Table 32: Summary of Harms in Study CL201 – Safety Analysis Set (up to 160 Weeks)

	Study CL201	
	Burosumab q.2.w. (N = 26)	Burosumab q.4.w. → q.2.w. (N = 26)
Patients with ≥ 1 AE		
n (%)	26 (100)	26 (100)
Most common events[a]		
Headache	20 (76.9)	19 (73.1)
Cough	21 (80.8)	15 (57.5)
Vomiting	13 (50.0)	16 (61.5)
Arthralgia	11 (42.3)	17 (65.4)
Nasopharyngitis	13 (50.0)	15 (57.7)
Pain in extremity	10 (38.5)	17 (65.4)
Injection-site reaction	13 (50.0)	13 (50.0)
Oropharyngeal pain	14 (53.8)	12 (46.2)
Pyrexia	12 (46.2)	13 (50.0)
URTI	12 (46.2)	13 (50.0)
Injection-site erythema	14 (53.8)	9 (34.6)
Rhinorrhea	12 (46.2)	10 (38.5)
Patients with ≥ 1 SAE		
n (%)	0	1 (3.8), 1 patient with pyrexia and myalgia
Patients with ≥ 1 WDAE		
n (%)	0	0
Deaths		
n (%)	0	0
Notable harms		
Injection-site reactions, n (%)	19 (73.1)	18 (69.2)
Hypersensitivity, n (%)	12 (46.2)	16 (61.5)
Hyperphosphatemia, n (%)	0	0
Ectopic mineralization, n (%)	1 (3.8)	0
Restless legs syndrome, n (%)	0	0

AE = adverse event; SAE = serious adverse event; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.4.w. → q.2.w. = every 4 weeks, then every 2 weeks; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

[a] Frequency > 40%.

Source: Clinical Study Report for Study CL201.[66]

Study CL303 Extension, up to Week 48

Study CL303 comprised a randomized, double-blind, placebo-controlled, 24-week treatment period; an open-label, 24-week treatment continuation period; an open-label treatment extension period I (48 weeks); and an open-label treatment extension period II (US only, up to 53 weeks).[12] As of the data cut-off date of the current Clinical Study Report (June 8, 2017), all study participants had completed the placebo-controlled period (week 24 visit) and the treatment continuation period (week 48 visit).

Methods

After completion of the 24-week, placebo-controlled treatment period, all patients — including those who were initially randomized to the placebo group —received open-label treatment with burosumab for 24 additional weeks until week 48. Patients and the investigators remained blinded to the original treatment allocations until week 48.

Populations

Study participants who had completed the placebo-controlled treatment period entered the 24-week treatment continuation period.

Interventions

Patients who had received burosumab in the 24-week, placebo-controlled treatment period continued burosumab treatment using the same dosing regimen of 1.0 mg/kg every four weeks (continuing on burosumab). Patients who received placebo in the placebo-controlled treatment period began receiving SC injections of burosumab (1.0 mg/kg) every four weeks in the treatment continuation period (placebo followed by burosumab).

Outcomes

Patient-reported outcomes, such as BPI pain scores, BFI scores, and WOMAC scores were measured at the end of the treatment continuation period (week 48). Efficacy outcomes related to phosphate homeostasis, bone metabolism, mobility, and occurrence of fractures and/or pseudofractures were evaluated at week 48. Harm outcomes, including AEs, SAEs, withdrawals due to AEs, and AEs of particular interest were reported at week 48 as well.

Statistical Analysis

The week 48 analysis was conducted after all patients had either completed the week 48 assessment or discontinued the study during the treatment continuation period. A GEE analysis was used for longitudinal analysis of efficacy end points repeatedly measured over time. The GEE model included treatment, actual randomization stratification factor based on BPI average pain (if applicable), region, visit, and interaction of treatment by visit as fixed factors, and was adjusted for baseline measurement.

The treatment continuation analysis set (defined as the subset of randomized patients who continued after the 24-week, placebo-controlled treatment period and received at least one dose of burosumab during the treatment continuation period) was used for the analysis of the efficacy and safety end points at week 48 analysis in addition to the PAS and SAS.

In general, no imputation of missing data was made for all analyses in Study CL303. When a change from baseline was assessed, only patients with a baseline and at least one post-baseline measurement were included in the analysis.

Patient Disposition

All but one patient completed the 24-week, placebo-controlled treatment period. The patient, who was in the burosumab group, withdrew consent for participation in the study. Of the 134 patients who enrolled in the study, 133 (67 in the continuing-on-burosumab group and 66 in the placebo-followed-by-burosumab group) received at least one dose of open-label burosumab and were included in the treatment continuation analysis set. Seven patients discontinued burosumab therapy during the treatment continuation period: four in the continuing-on-burosumab group and three in the placebo-followed-by-burosumab group.

Details of patient disposition during the treatment continuation period are provided in Table 33.

Table 33: Patient Disposition in Study CL303 – Week 48 Analysis (Week 24 to Week 48)

	Study CL303	
	Week 0 to week 24: burosumab; week 24 to week 48: continuing on burosumab	Week 0 to week 24: placebo; week 24 to week 48: switching to burosumab
Placebo-controlled treatment period (week 0 to week 24)		
Patients who completed placebo-controlled treatment period, n (%)	67 (98.5)	66 (100)
Discontinued during placebo-controlled treatment period, n (%)	1 (1.5)	0
Reason for discontinuation, n (%)		
Patient withdrew consent	1 (1.5)	0
Treatment continuation period (week 24 to week 48)		
Patients who completed treatment continuation period, n (%)	63 (92.6)	63 (95.5)
Discontinued during treatment continuation period, n (%)	4 (5.9)	3 (4.5)
Reason for discontinuation, n (%)		
Patient withdrew consent	1 (1.5)	0
Other	3 (4.4)	3 (4.5)
PAS, n (%)	68 (100)	66 (100)
SAS, n (%)	68 (100)	66 (100)
Treatment continuation analysis set, n (%)	67 (98.5)	66 (100)
Treatment extension analysis set, n (%)	63 (92.6)	63 (95.5)

PAS = primary analysis set; SAS = safety analysis set.

Source: Clinical Study Report for Study CL303.[12]

Exposure to Study Treatments

The mean duration of exposure to burosumab from week 0 to week 48 was 331 days for the patients who received 48-week burosumab therapy and 168 days for those who were treated with placebo during the first 24 weeks and then crossed over to burosumab for an additional 24 weeks. Details of study drug exposure are presented in Table 34.

Table 34: Extent of Exposure in Study CL303 – Safety Analysis Set (Week 0 to Week 48)

	Study CL303	
	Week 0 to week 24: burosumab; week 24 to week 48: continuing on burosumab (N = 68)	**Week 0 to week 24: placebo; week 24 to week 48: switching to burosumab (N = 66)**
Mean (SE)	330.7 (3.18)	168.1 (0.42)
Total patient-years of burosumab exposure[a]	61.56	30.38

SE = standard error.

[a] Total patient-years of exposure = sum of duration of exposure to burosumab (for all patients in each treatment group) ÷ 365.25.

Source: Clinical Study Report for Study CL303.[12]

Efficacy

At week 48, the LS mean changes in BPI worst pain scores from baseline were −1.1 (95% CI, −1.51 to −0.66; P < 0.0001) and −1.5 (95% CI, −1.98 to −1.09; P < 0.0001) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively, indicating a reduced intensity of the worst pain from baseline in both groups. However, the change in BPI worst pain was smaller than the MCID for this outcome (MCID = 2); therefore, the improvement in BPI worst pain was not considered clinically important. In addition, the LS mean (SE) changes in BPI pain severity scores and BPI pain interference scores were statistically significantly reduced from baseline in the continuing-on-burosumab group and the placebo-followed-by-burosumab groups at week 48, indicating an improvement in severity of pain and in the impact of pain on daily function in both groups.

At week 48, the LS mean (SE) changes in BFI worst fatigue scores from baseline were −1.0 (95% CI, −1.57 to −0.45; P = NR) and −1.2 (95% CI, −1.84 to −0.62; P = NR) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively, indicating a reduced worst fatigue intensity from baseline in both groups. In addition, the LS mean changes in BFI global fatigue scores from baseline were −0.5 (95% CI, −1.01 to 0.09; P = NR) and −0.7 (95% CI, −1.34 to −0.12; P = NR) for the continuing-on-burosumab group and the placebo-followed-by-burosumab groups, respectively, indicating an improvement in fatigue in both groups. However, a statistically significant change was not observed in the continuing-on-burosumab group.

Due to the lack of MCID for BPI pain severity, BPI pain interference, and BFI scales, the clinical importance of these improvements is unknown.

At week 48, the LS mean changes in WOMAC physical function scores from baseline were −7.8 (95% CI, −11.97 to −3.55; P = 0.0003) and −6.4 (95% CI, −11.94 to −0.76; P = 0.0259) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively, indicating an improvement in physical functioning in both groups from baseline. The LS mean changes in WOMAC stiffness scores from baseline were −16.0 (95% CI, −22.53 to −9.53; P < 0.0001) and −15.3 (95% CI, −22.23 to −8.35; P < 0.0001) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively, indicating an improvement in stiffness in both groups from baseline. Due to the lack of MCIDs for the WOMAC scores, the clinical importance of these improvements is unknown.

Details of patient-reported outcomes at week 48 are presented in Table 35.

Table 35: Patient-Reported Outcomes in Study CL303 – Primary Analysis Set

	Study CL303	
	Placebo followed by burosumab (N = 66)	Continuing on burosumab (N = 68)
BPI worst pain score, mean (SD)		
Number of patients analyzed, n	66	66
Baseline	6.54 (1.43)	6.81 (1.31)
Week 48	4.91 (2.13)	5.56 (1.90)
LS mean change from baseline Mean (SE) 95% CI P value	 −1.5 (0.23) −1.98 to −1.09 P < 0.0001	 −1.1 (0.22) −1.51 to −0.66 P < 0.0001
BPI pain severity score, mean (SD)		
Number of patients analyzed, n	66	66
Baseline	4.92 (1.55)	5.18 (1.53)
Week 48	3.63 (2.06)	4.19 (1.78)
LS mean change from baseline Mean (SE) 95% CI P value	 −1.2 (0.20) −1.58 to −0.81 NR	 −0.9 (0.16) −1.16 to −0.54 NR
BPI pain interference score, mean (SD)		
Number of patients analyzed, n	66	66
Baseline	4.76 (2.17)	5.23 (2.24)
Week 48	3.18 (2.39)	3.74 (2.28)
LS mean change from baseline Mean (SE) 95% CI P value	 −1.3 (0.25) −1.77 to −0.78 NR	 −1.0 (0.24) −1.51 to −0.56 NR
BFI worst fatigue score, mean (SD)		
Number of patients analyzed, n	66	66
Baseline	6.74 (1.53)	6.94 (1.66)
Week 48	5.31 (2.22)	5.64 (2.15)
LS mean change from baseline Mean (SE) 95% CI P value	 −1.2 (0.31) −1.84 to −0.62 NR	 −1.0 (0.29) −1.57 to −0.45 NR
BFI global fatigue score, mean (SD)		
Number of patients analyzed, n	66	66
Baseline	4.86 (1.93)	5.37 (2.04)
Week 48	3.55 (2.28)	4.17 (2.22)
LS mean change from baseline Mean (SE) 95% CI P value	 −0.7 (0.31) −1.34 to −0.12 NR	 −0.5 (0.28) −1.01 to 0.09 NR

	Study CL303	
	Placebo followed by burosumab (N = 66)	Continuing on burosumab (N = 68)
WOMAC physical function score, mean (SD)		
Number of patients analyzed, n	66	66
Baseline	43.9 (19.94)	50.8 (19.66)
Week 48	34.7 (22.62)	38.4 (18.61)
LS mean change from baseline, Mean (SE) 95% CI P value	 −6.4 (2.85) −11.94 to −0.76 P = 0.0259	 −7.8 (2.15) −11.97 to −3.55 P = 0.0003
WOMAC stiffness score, mean (SD)		
Number of patients analyzed, n	66	66
Baseline	61.4 (20.77)	64.7 (20.25)
Week 48	44.7 (22.47)	45.3 (21.90)
LS mean change from baseline, Mean (SE) 95% CI P value	 −15.3 (3.54) −22.23 to −8.35 P < 0.0001	 −16.0 (3.32) −22.53 to −9.53 P < 0.0001

BFI = Brief Fatigue Inventory; BPI = Brief Pain Inventory; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; NR = not reported; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Note: The GEE estimates were from the GEE model, which included the change from baseline for BPI, BFI, or WOMAC end point as the dependent variable; visit as a fixed factor; and baseline of BPI or BFI end point as covariate, with compound symmetry covariance structure.

Sources: Clinical Study Report for Study CL303.[12]

Phosphate Homeostasis

At the end of week 48, the LS mean changes from baseline in serum phosphorus concentration were 0.11 mmol/L (95% CI, 0.06 to 0.16) and 0.13 mmol/L (95% CI, 0.08 to 0.19) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group. The results at week 48 were similar to those at week 24. The proportion of patients with mean serum phosphorus above the LLN across midpoints of dose intervals was 83.8% in the continuing-on-burosumab group and 89.4% in the placebo-followed-by-burosumab group.

TmP/GFR in both groups increased from baseline. At week 48, the LS mean change from baseline in TmP/GFR was 0.52 mg/dL (95% CI, 0.33 to 0.72) and 0.61 mg/dL (95% CI, 0.42 to 0.79) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, representing percentage changes from baseline of 33.6% and 38.9%, respectively.

At week 48, the LS mean changes from baseline in TRP were 0.04 (95% CI, 0.02 to 0.05) and 0.03 (95% CI, 0 to 0.05) for the continuing-on-burosumab group and the placebo-followed-by-burosumab, representing percentage changes from baseline of 4.9% and 4.2%, respectively. The results at week 48 were similar to those at week 24.

There were no statistically significant changes observed from baseline for 24-hour urinary phosphorus in either group. The LS mean changes from baseline in 24-hour urinary phosphorus were 0.12 g/24hr (95% CI, –0.01 to 0.25) and 0.06 g/24hr (95% CI, –0.05 to 0.18) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively.

Serum $1,25(OH)_2D$ statistically significantly increased from baseline in both treatment groups at the end of week 48. The LS mean changes from baseline in $1,25(OH)_2D$ were 7.13 pg/mL (95% CI, 1.49 to 12.76) and 10.17 pg/mL (95% CI, 4.68 to 15.66) for the continuing-on-burosumab group and the placebo-followed-by-burosumab group, respectively.

Details of change in phosphate homeostasis are presented in Table 36.

Table 36: Results of Phosphate Homeostasis in Study CL303 – Primary Analysis Set

	Study CL303	
	Placebo followed by burosumab (N = 66)	Continuing on burosumab (N = 68)
Serum phosphorus, mmol/L, mean (SD)		
Number of patients analyzed, n	66	63
Baseline	0.617 (0.1001)	0.653 (0.1072)
Week 24	0.668 (0.1152)	0.818 (0.1465)
Week 48	0.800 (0.1664)	0.794 (0.1554)
LS mean change from baseline, mean (95% CI) P value	0.13 (0.08 to 0.19) P value NR	0.11 (0.06 to 0.16) P value NR
% of patients with mean serum phosphorus > LLN across midpoints of dose intervals, %		
Yes	89.4	83.8
TmP/GFR, mg/dL, mean (SD)		
Number of patients analyzed, n	62	61
Baseline	1.60 (0.37)	1.68 (0.40)
Week 24	1.73 (0.42)	2.22 (0.49)
Week 48	2.21 (0.59)	2.20 (0.52)
LS mean change from baseline, mean (95% CI), P value	0.61 (0.42 to 0.79) P value NR	0.52 (0.33 to 0.72) P value NR
LS mean % change from baseline, mean (95% CI) P value	38.9 (27.52 to 50.31) P value NR	33.6 (22.10 to 45.16) P value NR
TRP, mean (SD)		
Number of patients analyzed, n	64	63
Baseline	0.81 (0.08)	0.81 (0.08)
Week 24	0.80 (0.12)	0.84 (0.06)
Week 48	0.84 (0.09)	0.85 (0.07)
LS mean change from baseline, mean (95% CI) P value	0.03 (0 to 0.05)	0.04 (0.02 to 0.05)
LS mean % change from baseline, mean (95% CI) P value	4.2 (0.78 to 7.61) P value NR	4.9 (2.42 to 7.38) P value NR
24-hr urinary phosphorus, g/24 hr, mean (SD)		
Number of patients analyzed, n	63	63
Baseline	0.81 (0.26)	0.72 (0.24)
Week 24	0.77 (0.36)	0.72 (0.31)
Week 48	0.79 (0.34)	0.80 (0.53)
LS mean change from baseline, mean (95% CI)	0.06 (–0.05 to 0.18)	0.12 (–0.01 to 0.25)

	Study CL303	
	Placebo followed by burosumab (N = 66)	Continuing on burosumab (N = 68)
P value	P value NR	P value NR
LS mean % change from baseline, mean (95% CI) P value	25.92 (–0.39 to 52.23) P value NR	36.66 (9.55 to 63.76) P value NR
Serum $1,25(OH)_2D$, pg/mL, mean (SD)		
Number of patients analyzed, n	64	63
Baseline	33.5 (15.61)	32.4 (12.96)
Week 22 (midpoint of dose interval)	34.9 (14.52)	57.0 (18.02)
Week 48 (end-of-dose interval)	41.9 (13.42)	38.0 (13.62)
LS mean change from baseline, mean (95% CI)	10.17 (4.68 to 15.66)	7.13 (1.49 to 12.76)
LS mean % change from baseline, mean (95% CI)	69.35 (30.94 to 107.76)	34.91 (6.14 to 63.69)

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; CI = confidence interval; GEE = generalized estimating equation; NR = not reported; LLN = lower limit of normal; LS = least squares; SD = standard deviation; TmP/GFR = ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate; TRP = tubular reabsorption of phosphate.

Note: Estimates of LS means and P values were based on the GEE model, which included the change from baseline or percentage change from baseline for serum phosphorus (or TmP/GFR, TRP, or 24-hour urinary phosphorus) as the dependent variable; region, visit, treatment, actual randomization stratification, and visit by treatment as fixed factors; and baseline of serum phosphorus (or TmP/GFR, TRP, 24-hour urinary phosphorus, or $1,25(OH)_2D$) as covariate, with compound symmetry covariance structure.

Source: Clinical Study Report for Study CL303.[12]

Bone Metabolism

At the end of week 48, statistically significant increases from baseline in P1NP and CTx were observed in both the continuing-on-burosumab group and placebo-followed-by-burosumab group. The change in BALP from baseline was not statistically significant in the continuing-on-burosumab group.

Details of bone metabolism biomarkers are presented in Table 37.

Table 37: Results of Bone Metabolism in Study CL303 – Primary Analysis Set

	Study CL303	
	Placebo followed by burosumab (N = 66)	Continuing on burosumab (N = 68)
Serum P1NP, ng/mL, mean (SD)		
Number of patients analyzed, n	64	57
Baseline	87.8 (53.3)	85.2 (50.7)
Week 48	174.1 (132.46)	130.1 (68.82)
LS mean change from baseline, mean (95% CI)	76.90 (54.90 to 98.89)	35.68 (17.50 to 53.85)
LS mean % change from baseline, mean (95% CI)	95.72 (72.23 to 119.22)	56.14 (35.50 to 76.78)
Serum CT_X, pg/mL, mean (SD)		
Number of patients analyzed, n	64	56
Baseline	720.5 (417.91)	702.4 (395.54)
Week 48	1,051.0 (654.99)	876.5 (423.62)
LS mean change from baseline, mean (95% CI)	295.94 (200.79 to 391.09)	127.13 (36.72 to 217.54)

	Study CL303	
	Placebo followed by burosumab (N = 66)	Continuing on burosumab (N = 68)
LS mean % change from baseline, mean (95% CI)	49.16 (35.43 to 62.89)	28.91 (17.65 to 40.17)
BALP concentration, mcg/mL, mean (SD)		
Number of patients analyzed, n	64	55
Baseline	24.7 (17.25)	24.0 (19.68)
Week 48	31.2 (19.36)	26.4 (19.42)
LS mean change from baseline, mean (95% CI)	6.65 (2.63 to 10.68)	1.23 (–2.30 to 4.77)
LS mean % change from baseline, mean (95% CI)	50.21 (27.11 to 73.31)	23.65 (3.02 to 44.27)

BALP = bone-specific alkaline phosphatase; CI = confidence interval; CTx = carboxy terminal cross-linked telopeptide of type 1 collagen; GEE = generalized estimating equation; LS = least squares; P1NP = procollagen type 1 N-propeptide; SD = standard deviation.

Note: LS means and P values were based on the GEE model, including the change from baseline and percentage change from baseline as dependent variables; region, visit, treatment, actual randomization stratification, and visit by treatment as fixed factors; and baseline value as covariate, with compound symmetry covariance structure.

Source: Clinical Study Report for Study CL303.[12]

Mobility Measurement – 6-Minute Walk Test Distance Change From Baseline

At the end of week 48, an increase from baseline in the distance walked in six minutes was observed in both treatment groups. For the continuing-on-burosumab group, the LS mean change from baseline in the distance walked was 30.5 m (95% CI, 16.9 to 44.1), a statistically and clinically significant improvement, given an MCID of 31 m for the 6MWT in adult patients. For the placebo-followed-by-burosumab group, the LS mean change from baseline in the distance walked was 20 m (95% CI, 3.0 to 37.4), a statistically but not clinically significant improvement, given an MCID of 31 m for the 6MWT in adult patients.

Details of the 6MWT are presented in Table 38.

Table 38: Results of Mobility in Study CL303 – Primary Analysis Set

	Study CL303	
	Placebo followed by burosumab (N = 66)	Continuing on burosumab (N = 68)
6MWT distance, m, mean (SD)		
Number of patients analyzed, n	65	63
Baseline	367.4 (103.41)	356.8 (109.46)
Week 24	369.4 (103.39)	381.5 (108.46)
Week 48	390.9 (106.51)	392.5 (107.15)
LS mean change from baseline to week 48, mean (95% CI)	20.2 (3.02 to 37.35)	30.5 (16.92 to 44.08)

6MWT = 6-minute walk test; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SD = standard deviation.

[a] Patients in the q.4.w. group were to switch to the q.2.w. group beginning with week 64 dosing.

Note: The GEE model included change in 6MWT score as the dependent variable; visit, regimen, and visit by regimen as factors; and 6MWT at baseline as covariate, with exchangeable covariance structure.

Source: Clinical Study Report for Study CL303.[12]

Fracture or Pseudofractures

At week 48, 72.4% of patients in the continuing-on-burosumab group with active pseudofractures at baseline had full healing compared to 52.9% of those in the placebo-followed-by-burosumab group. For 27.5% and 32.3% of the patients with baseline active pseudofractures, their condition remained unchanged or worsened. For the patients with active fractures at baseline, 50% had full healing at week 48 in both groups, while 37.5% in the continuing-on-burosumab group and 25% in the placebo-followed-by-burosumab group remained unchanged or worsened. One new active fracture was reported in the placebo-followed-by-burosumab group during the treatment continuation period.

Details of change in pseudofractures and fractures in the treatment continuation period are presented in Table 39.

Table 39: Results of Change in Number of Patients With Fractures or Pseudofractures in Study CL303 – Primary Analysis Set

	Study CL303	
	Placebo followed by burosumab (N = 66)	Continuing on burosumab (N = 68)
Active pseudofracture, n (%)		
Patients with active pseudofractures at baseline, n	34	29
Patients with pseudofractures at week 48, n (% baseline)		
Healed	18 (52.9)	21 (72.4)
Partially healed	19 (55.9)	7 (24.1)
Unchanged	7 (20.6)	3 (10.3)
Worse	3 (8.8)	2 (6.9)
Missing	1 (2.9)	3 (10.3)
New finding	0	0
Active fracture, n (%)		
Patients with active fractures at baseline, n	8	8
Patients with fractures at week 48, n (% baseline)		
Healed	4 (50.0)	4 (50.0)
Partially healed	3 (37.5)	2 (25.0)
Unchanged	1 (12.5)	1 (12.5)
Worse	0	0
Missing	1 (12.5)	2 (25.0)
New finding	1 (1.5)[a]	0

[a] Percentage was calculated based on N.

Source: Clinical Study Report for Study CL303.[12]

Harms

By the data cut-off date of June 8, 2017, all patients in the continuing-on-burosumab group and 95.5% of the patients in the placebo-followed-by-burosumab group reported at least one AE. The majority of the AEs were grade 1 or grade 2. The most commonly reported AEs included arthralgia (23.9%), nasopharyngitis (22.4%), headache (20.1%), back pain (16.4%), tooth abscess (13.4%), and fatigue (13.4%).

There were seven patients (10.3%) in the continuing-on-burosumab group and eight patients (12.1%) in the placebo-followed-by-burosumab group who reported SAEs. There were no patients who withdrew from the study or from treatment due to AEs. No deaths were reported by the data cut-off date.

The AEs of particular interest included ISRs (20.1%), hypersensitivity (11.2%), hyperphosphatemia (6.0%), ectopic mineralization (6.7%), and restless legs syndrome (11.9%).

Details of the safety evaluation are presented in Table 40.

Table 40: Summary of Harms in Study CL303 – SAS (Through Data Cut-Off Date of June 8, 2017)

	Study CL303	
	Placebo followed by burosumab (N = 66)[a]	Continuing on burosumab (N = 68)[b]
Patients with ≥ 1 AE		
n (%)	63 (95.5)	68 (100)
Most common events[c]		
Arthralgia	15 (22.7)	17 (25.0)
Nasopharyngitis	10 (15.2)	20 (29.4)
Headache	9 (13.6)	18 (26.5)
Back pain	11 (16.7)	11 (16.2)
Tooth abscess	3 (4.5)	15 (22.1)
Fatigue	6 (9.1)	12 (17.6)
Pain	6 (9.1)	9 (13.2)
Toothache	6 (9.1)	9 (13.2)
Pain in extremity	6 (9.1)	9 (13.2)
Restless legs syndrome	6 (9.1)	9 (13.2)
Musculoskeletal pain	4 (6.1)	10 (14.7)
Vitamin D deficiency	4 (6.1)	10 (14.7)
Diarrhea	3 (4.5)	9 (13.2)
Nausea	4 (6.1)	8 (11.8)
Procedural pain	4 (6.1)	7 (10.3)
Injection-site reaction	4 (6.1)	7 (10.3)
Dizziness	2 (3.0)	8 (11.8)
Myalgia	2 (3.0)	7 (10.3)
Depression	2 (3.0)	7 (10.3)
Patients with ≥ 1 SAE		
n (%)	8 (12.1)	7 (10.3)
	Presyncope, palpitations, arthralgia, cervical spinal stenosis, decrease in joint range of motion, periodontal disease, pseudarthrosis, and subdural hematoma	Cholelithiasis, colitis, procedural nausea/vomiting, myelopathy/ spinal column stenosis, and musculoskeletal pain

	Study CL303	
	Placebo followed by burosumab (N = 66)[a]	Continuing on burosumab (N = 68)[b]
Patients with ≥ 1 WDAE		
n (%)	0	0
Deaths		
n (%)	0	0
Notable harms		
Injection-site reactions, n (%)	8 (12.1)	19 (27.9)
Hypersensitivity, n (%)	4 (6.1)	11 (16.2)
Hyperphosphatemia, n (%)	4 (6.1)	4 (5.9)
Ectopic mineralization, n (%)	5 (7.6)	4 (5.9)
Restless legs syndrome, n (%)	6 (9.1)	10 (14.7)

AE = adverse event; SAE = serious adverse event; SAS = safety analysis set; WDAE = withdrawal due to adverse event.

[a] Treatment continuation or treatment extension period.

[b] Any period.

[c] Frequency > 10%.

Source: Clinical Study Report for Study CL303.[12]

Critical Appraisal

Internal Validity

The efficacy and safety of longer-term burosumab therapy were evaluated in the extension periods of studies CL201 and CL303, which enrolled children five years to 12 years of age and adults with XLH, respectively. In the extension periods of both studies, all participants received burosumab for an additional 24 weeks to 96 weeks. In Study CL201, all patients from the original randomization period entered the extension period and completed the additional 96-week treatment. In Study CL303, the vast majority of the patients (> 90%) who were enrolled in the original double-blind randomization period remained in the study and completed the additional 24-week treatment. In Study CL201, a single, central, independent rater performed all RSS ratings for all radiographs. In Study CL303, blood or urine samples for relevant outcomes — such as serum phosphorus, bone turnover markers, and $1,25(OH)_2D$ — were sent to central labs for assessment.

The main limitations associated with the extension periods of the two studies arise from their open-label study design, lack of randomization, and within-group comparisons to baselines. These limitations may have an impact on the subjective patient-reported questionnaires concerning pain, fatigue, and physical function, such as the BPI, BFI, or WOMAC. Furthermore, the absence of a comparator group makes it challenging to interpret small changes from baseline.

The absence of a comparator group also makes it challenging to interpret small changes from baseline, particularly in the long-term study of children (Study CL201), where maturation may be responsible for changes in the relevant outcomes.

External Validity

There was lack of information about the use of burosumab in the adolescent population, as no clinical trials in the burosumab development program enrolled patients aged 13 years to 17 years.

Patients enrolled in the trials appear to be similar, in general, to patients with XLH in Canada.

Conclusions

The results of the extension periods of Study CL201 (for pediatric patients) and Study CL303 (for adults) suggest that the efficacy of burosumab was maintained throughout an additional 24 weeks to 96 weeks of treatment. Continuous treatment with burosumab was associated with reduced severity of rickets, improved pain, improved fatigue, improved walking ability, and increased serum phosphorus levels for patients five years to 12 years of age and adults. Almost all patients experienced AEs in the extension periods. Most were mild to moderate in intensity. The AEs most commonly reported in the pediatric population included headache, cough, vomiting, arthralgia, and nasopharyngitis, while in adults, the most commonly reported AEs were arthralgia, nasopharyngitis, and headache. The risk of SAEs was low. There were no new safety signals during the extension period for either patient group. Due to the non-randomized and uncontrolled, open-label study design, there is a high degree of uncertainty with respect to the findings of the extension studies.

Discussion

Summary of Available Evidence

A total of four studies met the inclusion criteria: Study CL301, Study CL201, Study CL205, and Study CL303. Study CL301 was a randomized, open-label, phase III study comparing the efficacy and safety of burosumab to active control (oral phosphate and active vitamin D therapy) in children (one year to ≤ 12 years of age) with clinical evidence consistent with XLH and a confirmed PHEX mutation (in the patient or direct relative) or variants of unknown significance. Study CL201 was a pivotal, open-label, dose-finding, phase II study to assess the efficacy and safety of burosumab in prepubescent children (five years to 12 years old) with XLH. Study CL205 was a pivotal, open-label, single-arm, phase II study to assess the efficacy and safety of burosumab in children from one year to four years of age with XLH who were naive to therapy or had previously received standard therapy with oral phosphate and active vitamin D. Study CL303 was a pivotal, randomized, double-blind, placebo-controlled, phase III study that evaluated the efficacy and safety of burosumab in adult patients with XLH. Change in rickets at week 40 as assessed by RGI-C global score was the primary outcome in Study CL301. Change from baseline in severity of rickets as measured by RSS total score was the primary outcome in Study CL201. Change from baseline in serum phosphorus at week 40 was the primary outcome in Study CL205. The proportion of patients achieving mean serum phosphorus levels above the LLN was the primary outcome in Study CL303.

In addition to the main studies reviewed, the long-term extensions of studies CL201 and CL303 — and of Study CL304, which was a phase III, open-label, single-arm, ongoing study designed to assess the effectiveness and safety of burosumab treatment on bone quality and osteomalacia associated with XLH for adult patients — were reviewed and critically appraised. Safety results are reported in the Other Relevant Studies section.

Interpretation of Results

Efficacy

Patients with XLH have a spectrum of rickets severity based on varying degrees of phosphorus metabolic defect and degree of prior treatment. To evaluate the spectrum of abnormalities, two radiographic scoring methods, the RGI-C and the RSS, were used in studies CL301, CL201, and CL205. These instruments provide complementary analyses of the severity of rickets based on evaluations of epiphyseal and distal metaphyseal abnormalities in wrist and knee radiographs. The RGI-C method used also provides an evaluation of deformities observed in standing long leg radiographs. The use of these tools was deemed adequate to demonstrate clinical efficacy in children by Health Canada reviewers,[8] despite some shortcomings (e.g., no sufficient data demonstrating clinically meaningful difference threshold, MCIDs, or lack of fully independent validation in patients with XLH). The mean baseline values for the RSS were quite different among studies CL301 (3.18), CL201 (1.92), and CL205 (2.92), indicating a significantly different severity of disease among the pediatric populations included in these studies. Higher RSS total scores indicate more severe rickets; an RSS of 1.5 is perceived to be quite mild.

In Study CL301, assessments using the RSS method showed greater reductions in the severity of rickets with burosumab treatment. The mean RSS total score decreased in the burosumab group from 3.17 at baseline to 1.13 at week 40, compared with a decrease in

the active-control group from 3.19 to 2.47. This reduction was maintained at week 64. The difference in RSS total scores for change from baseline were statistically significant at week 40 (−1.34 [95% CI, −1.74 to −0.94; P < 0.0001]) and at week 64 (−1.21 [95% CI, −1.59 to −0.83; P < 0.0001]). Similar decreases in rickets severity were observed for mean RSS knee scores and mean RSS wrist scores at both week 40 and week 64.

The other two studies of pediatric patients (Study CL201 and Study CL205) did not have active comparator arms. Despite notable difference in baseline severity (RSS total scores of 1.92 and 2.92 in the CL201 and CL205 studies, respectively), pediatric patients who received burosumab every two weeks showed consistent improvements, as demonstrated by within-group changes from baseline to week 40 in RSS total scores (−1.06 [95% CI, −1.28 to −0.85; P < 0.0001] in Study CL201 and −1.73 [95% CI, −2.03 to −1.44; P < 0.0001] in Study CL205). In Study CL301, the within-group change from baseline to week 40 in RSS total score was −2.04.

In Study CL301, the LS mean RGI-C global scores at week 40 were 1.92 in the burosumab group and 0.77 in the active-control group, a statistically significant difference of 1.14 (95% CI, 0.83 to 1.45; P < 0.0001); this improvement was maintained at week 64 (1.02 [95% CI, 0.72 to 1.33]; P < 0.0001). Greater healing in the burosumab group compared with the active-control group was also observed in RGI-C knee and wrist scores at both week 40 and week 64. Burosumab treatment resulted in substantial healing of rickets (defined as an RGI-C global score ≥ +2.0) in 72% of patients at week 40 as compared with 6% of patients treated with active control; this difference was maintained at week 64. Skeletal abnormalities of the lower extremities, assessed by RGI-C in standing long leg radiographs, also showed greater healing in the burosumab group than in the active-control group. At week 64, the LS mean RGI-C lower limb deformity scores were 1.25 in the burosumab group and 0.29 in the active-control group, a mean difference of 0.97 (95% CI, 0.57 to 1.37; P < 0.0001). However, no MCIDs were identified for the RSS or RGI-C for patients with XLH; therefore, the clinical importance of the improvement in these outcomes is unknown.

In Study CL301, differences between the treatment groups in RGI-C global scores and RSS total scores were analyzed in subgroups of baseline rickets severity (RSS total score ≤ 2.5 versus > 2.5) and age (< five years versus ≥ five years). The results in the subgroups were similar to those of the overall study population.

It is worth noting that all of analyses for RSS and RGI-C scores (except for the primary efficacy end point in studies CL301, CL201, and CL205) were not adjusted for multiplicity. Any result reported should be interpreted with consideration of the potential for inflated type I error.

Growth impairment is one of the predominant features of children with XLH. Analyses of change in standing height or recumbent length (z score, percentile for age and gender, growth velocity [cm/year], and growth velocity z score) in Study CL301 showed growth in both treatment groups. However, the clinical experts consulted for this review indicated that the differences reported between the treatment groups at week 40 and week 64 were small. They are not considered clinically relevant, given the short time frame of the study.

The chronic hypophosphatemia experienced by patients with XLH leads to rickets and osteomalacia, the two major pathologic features of XLH in bone; therefore, one of the goals of therapy is to increase serum phosphorus concentrations to normal or close to normal. Change in serum phosphorus concentrations was a secondary efficacy end point in Study CL301, while the proportion of patients achieving mean serum phosphorus levels above the

LLN (0.81 mmol/L) was the primary efficacy end point in Study CL303. In Study CL301, of the 29 patients randomized to the burosumab treatment group, 17 patients (58.6%) and 19 patients (65.5%) had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40 and week 64, respectively. Of the 32 patients randomized to the active-control group (oral phosphate and active vitamin D therapy), only one patient (3.1%) had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40 and week 64. In the subgroup of patients younger than five years of age, nine patients (64.3%) in the burosumab treatment group had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) versus none in the active-control group. In the subgroup of patients five years of age and older, eight patients (53.3%) in the burosumab treatment group had a serum phosphorus concentration within the normal range (1.03 mmol/L to 1.97 mmol/L) versus one patient (5.0%) in the active-control group. No statistical comparison between the two treatment groups was conducted.

It is worth noting that no reference was provided for the normal range of serum phosphorus used in Study CL301 of 1.03 mmol/L to 1.97 mmol/L. The clinical experts consulted for this review indicated that they use the numbers provided in the CALIPER Database,[9] which provides biochemical markers across the pediatric age (birth to 18 years). This database indicates that the normal range of serum phosphorus for the age group one year to less than five years of age is higher than the range for the age group five years to less than 13 years of age. In addition, none of the measures reported in the CALIPER Reference Interval Database[9] had the lower bound for the age group one year to less than five years at 1.03 mmol/L (the lowest reported is 1.26 mmol/L). The sponsor clarified that the serum phosphorus levels were determined according to the standards in place in local laboratories. However, the normal range of serum phosphorus used was the same regardless of age; hence, there is uncertainty around the number of patients who actually achieved a normal range of serum phosphorus for patients who were younger than five years of age.

Study CL303 was the only one with a relatively large sample size (N = 134) that studied adult patients. Patients enrolled were required to have hypophosphatemia at screening (i.e., a serum phosphorus concentration < 0.81 mmol/L), as expected for patients with XLH. The primary end point for this study was the proportion of patients achieving mean serum phosphorus levels above the LLN (0.81 mmol/L) at the midpoint of the dose interval, as averaged across dose cycles between baseline and week 24. Study CL303 demonstrated a statistically significant effect of burosumab relative to placebo in increasing serum phosphorus concentrations from baseline to week 24, with a total of 94.1% of patients in the burosumab group achieving a mean serum phosphorus concentration above the LLN (0.81 mmol/L) across the midpoints of the dose intervals through week 24, compared with only 7.6% of patients in the placebo group (P < 0.0001). The mean change from baseline across the midpoints of the dose cycles to week 24 in the burosumab group was 0.39 mmol/L, compared with only 0.05 mmol/L in the placebo group.

Mobility in Study CL301 was assessed using the 6MWT and PROMIS score for physical function mobility scales in patients greater than or equal to five years of age. The difference in 6MWT between the treatment groups for the change from baseline to week 40 was 43 m (95% CI, −0.3 to 87; P = 0.0514), which was not statistically significantly different. At week 64, it was 46 m (95% CI, 2 to 89; P = 0.0399) in favour of burosumab. The difference between treatment groups exceeded the MCID established for patients with hypophosphatasia (31 m for children and adults; 43 m for adolescents). However, initial

improvements in the 6MWT should be interpreted with caution, as there is a well-documented learning effect in patients previously unfamiliar with the test.[67] Motivation, encouragement, and co-operation can have a significant positive impact on the results, and the magnitude of these effects could be comparable to the effect of interventions.[68,69] This could be of special concern in situations where blinding is not present or is compromised. On the other hand, the PROMIS score for physical function mobility scales did not show statistically significant differences between the treatment groups, where the change from baseline was 2.68 (95% CI, −0.52 to 5.89; P = 0.1009) at week 40 and 1.90 (95% CI, −1.80 to 5.59; P = 0.3145) at week 64. In addition, an MCID for the PROMIS score for physical function mobility scales was not identified; therefore, the clinical importance of the improvement in this outcome is unknown.

Mobility in Study CL303 was assessed using the 6MWT and WOMAC physical function. The difference in the 6MWT between treatment groups for the change from baseline to week 24 was 19.93 m (95% CI, 4 to 36; P = 0.0120) in favour of burosumab; however, this difference between treatment groups may not be clinically relevant, given that it did not exceed the established MCID of 31 m for patients with hypophosphatasia. In addition, 6MWT results were not adjusted for multiplicity; any result reported should be interpreted with consideration for the potential for inflated type I error. Also, while WOMAC physical function impairment favoured burosumab, the differences between the burosumab and placebo groups at week 24 were not statistically significant after multiplicity adjustment. In addition, due to the lack of an MCID for the WOMAC, the clinical importance of these improvements is unknown.

Pain (including bone pain, joint pain and joint stiffness, and dental pain) was included in this systematic review to provide a patient perspective on treatment with burosumab. Pain in Study CL301 was assessed using the FPS-R and the PROMIS pain interference in patients who were at least five years of age. No notable change between treatment groups was reported. It is worth noting that for these outcomes, only 15 patients were included in the burosumab group and 20 in the active-control group. These very small sample sizes mean that strong inferences cannot be drawn about any between-group differences.

In Study CL303, WOMAC stiffness and BPI were used to assess pain and stiffness. While the burosumab group had a statistically significant decrease from baseline in WOMAC stiffness scores relative to the placebo group at week 24 (the LS mean difference between treatment groups at week 24 was −8.31 [95% CI, −14.68 to −1.94; P = 0.0106]), there is no MCID established for this scale. As a result, the clinical importance of these improvements is unknown. Results in BPI worst pain did not show statistically significant differences between burosumab and placebo groups at week 24 after multiplicity adjustment. (The LS mean difference between treatment groups at week 24 was −0.46 [95% CI, −1.00 to 0.08; P = 0.0919]). In addition, the BPI pain severity score and BPI pain interference did not show differences between burosumab and placebo treatment groups: for pain severity, the LS mean difference between treatment groups at week 24 was −0.43 (95% CI, −0.93 to 0.07; P = 0.0926), and for pain interference, the LS mean difference between treatment groups at week 24 was −0.13 (95% CI, −0.70 to 0.44; P = 0.6511). The clinical experts indicated that the duration of the study (24 weeks) might have been too short to notice any improvement in pain, and that the lack of patient-reported improvements in physical function or pain was likely to reflect the multifactorial nature of XLH presentation in adults.

Fatigue was also considered an important outcome to patients, as reported in the patient group input section. Fatigue was assessed using the PROMIS fatigue t score in Study

CL301 and using the BFI in Study CL303. In Study CL301, no difference between the burosumab group and the active-control group was found in fatigue t score. Similarly, no difference between the burosumab group and the placebo group was reported in Study CL303 study for the BFI worst fatigue score, where the LS mean difference between treatment groups at week 24 was −0.20 (95% CI, −0.80 to 0.40; P = 0.5150). For the BFI global fatigue score, the LS mean difference between treatment groups at week 24 was 0.11 (95% CI, −0.46 to 0.67; P = 0.7129). This would likely indicate that there was no improvement in fatigue using burosumab treatment.

HRQoL measures were also included in this systematic review to provide a patient perspective on treatment with burosumab. The SF-10 PHS and PSS were exploratory efficacy end points in Study CL301, and no statistical significance test for comparison between the two treatment groups was conducted. Hence, no statistical inference could be drawn as to whether burosumab improved HRQoL comparing to phosphate and active vitamin D therapy.

It is worth noting that Study CL301 was open-label. There is a risk of bias with outcomes measured in open-label studies because patients and providers are aware of their assigned interventions. Measurement of subjective outcomes (such as HRQoL) may be at increased risk of bias if patients in the study are aware of their treatment allocation.

Fractures and pseudofractures were also considered important outcomes to patients, as reported in the patient input section. While Study CL303 was not designed to emphasize differences in fractures and pseudofractures, these end points are clinically important. At week 24, 50% (16 out of 32) patients in the burosumab group had full healing of at least one active fracture or pseudofracture compared with 13% (5 out of 38) patients in the placebo group. However, the presence of fractures and pseudofractures appeared to have no relationship with pain scores at baseline. In addition, an FDA analysis suggested that radiographic healing was not a strong predictor of relief from pain.[2] Therefore, the clinical significance of improved fracture healing was somewhat unclear with regards to alleviation of pain, but was not inconsistent with the view that pain in XLH is multifactorial and arises from a combination of long-standing disease manifestations (enthesopathy) as well as potentially treatable elements (such as osteomalacia and fractures and/or pseudofractures).

The results of a single-arm, open-label study (Study CL304) including 14 patients suggested that 48-week treatment with burosumab was associated with improvement in osteomalacia, patient-reported pain and fatigue, serum phosphorus levels, and bone metabolism biomarkers in adult patients with XLH. Three out of four pseudofractures at baseline were healed at the end of 48-week treatment. Due to the uncontrolled study design and high degree of uncertainty related to the small sample size, the study results should be interpreted with caution.

The results of the extension periods of Study CL201 (for pediatric patients) and Study CL303 (for adults) suggested that the efficacy of burosumab was maintained throughout an additional 24 weeks to 96 weeks of treatment. Continuous treatment with burosumab was associated with reduced severity of rickets, improved pain, improved fatigue, improved walking ability, and increased serum phosphorus levels for patients aged five years to 12 years old and adults. Almost all patients experienced AEs in the extension periods. Most of the AEs were mild to moderate in intensity. Due to the non-randomized and uncontrolled open-label study design, there is a high degree of uncertainty with respect to the findings of the extension studies.

There are uncertainties in the clinical evidence of burosumab, including a lack of evidence in young people aged 13 years to 17 years. A long-term benefit has not been established, yet burosumab is a potentially lifelong treatment. XLH is heterogenous in terms of both symptoms and severity, and it is unclear which patients will benefit most. It is also unknown whether burosumab treatment would prevent pseudofractures and fractures. Furthermore, it is unclear how treatment benefit may differ in adult patients who first receive burosumab during adulthood compared with a future cohort of adult patients who may receive burosumab treatment throughout childhood.

Harms

The overall frequency of TEAEs was similar between studies for those who received burosumab. AEs were reported by all patients who received burosumab in studies CL301, CL201, and CL205, and by 94.1% of patients who received burosumab in Study CL303. In Study CL301, 84% (27 out of 32) of the patients in the active-control group experienced at least one TEAE. In Study CL303, 92.4% (61 out of 66) of the patients in the placebo group experienced at least one TEAE.

The safety profile did not raise any serious concerns. The number of SAEs was low in all of the included studies; no patient withdrew from treatment or from the studies for AEs; and no deaths were reported during the studies. In Study CL301, 15 patients in the burosumab group (52%) experienced ISRs. Hypersensitivity TEAEs were experienced by 11 patients (38%) in the burosumab group and by six patients (19%) in the active-control group. No TEAEs of hyperphosphatemia, ectopic mineralization, or restless leg syndrome were reported in either treatment group. In Study CL303, eight patients (11.8%) in the burosumab group and eight patients (12.1%) in the placebo group experienced TEAEs of ISRs. Hypersensitivity was reported by four patients in each treatment group (burosumab: 5.9%; placebo: 6.1%). TEAEs involving hyperphosphatemia were reported for four patients (5.9%) in the burosumab group and none in the placebo group. A total of eight patients (11.8%) in the burosumab group and five patients (7.6%) in the placebo group had a TEAE of restless leg syndrome or limb discomfort (13.5%). No TEAEs involving ectopic mineralization were reported in either treatment group during the double-blind period. In studies CL301 and CL303, most of the AEs of special interest were considered mild or moderate, and none led to discontinuation of study drug.

In Study CL304, all patients experienced AEs, although the majority were mild to moderate in severity. There were no unexpected safety signals in the study population.

In the extension periods of studies CL201 and CL303, the AEs most commonly reported in pediatric population included headache, cough, vomiting, arthralgia, and nasopharyngitis, while in adults, the most commonly reported AEs were arthralgia, nasopharyngitis, and headache. The risk of SAEs was low. There were no new safety signals during the extension period for either patient group.

Conclusions

Studies CL301 and CL303 provided evidence of the efficacy and safety of burosumab in pediatric patients and adult patients with XLH, respectively. Pediatric patients who received burosumab every two weeks showed improvements in radiographic end points (as measured by the RSS and RGI-C), serum phosphorus concentrations, and lower extremity deformities. However, there was uncertainty with regard to improvements in growth and mobility compared with oral phosphate and active vitamin D treatment. In addition, burosumab was not associated with meaningful improvement in HRQoL or other important patient-reported outcomes. Long-term extension studies support the sustainability of these treatment effects.

In adult patients, burosumab was associated with significant improvements in serum phosphorus concentration and patient-reported stiffness compared to placebo at week 24. There were also likely clinically significant improvements in patients receiving burosumab in terms of the healing of active and non-active fractures and pseudofractures compared to placebo. However, when compared with placebo, burosumab did not show improvement in pain or fatigue.

In both pediatric and adult patients, no patients withdrew from treatment or from the studies for AEs, and no deaths were reported during the studies or their extension periods. There were no safety signals of special interest among reported AEs (including hyperphosphatemia, ectopic mineralization, hypersensitivity, and ISRs). Safety data from the studies did not demonstrate any notable concern about SAEs. Conclusions regarding the long-term efficacy and safety of burosumab in patients with XLH are limited due to the short treatment durations. Ideally, several more years of treatment with follow-up would highlight whether burosumab offers long-term improvement and a better safety profile compared to the current conventional therapy.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	August 14, 2019
Alerts:	Weekly search updates until project completion
Study Types:	No filters were applied to limit retrieval by study type
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.ot	Original title
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(crysvita* or burosumab* or krn 23 or krn23 or G9WJT6RD29).ti,ab,kf,ot,hw,nm,rn.
2	1 use medall
3	*burosumab/ or (crysvita* or burosumab* or krn 23 or krn23).ti,ab,kw,dq.
4	3 use oemezd
5	(Conference abstract or conference review).pt.
6	4 not 5
7	2 or 6
8	remove duplicates from 7

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Crysvita, burosumab, krn 23, krn23
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Crysvita, burosumab, krn 23, krn23

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	August 2019
Keywords:	Crysvita (burosumab), X-linked hypophosphatemia
Limits:	none

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Internet Search

Appendix 2: Excluded Studies

Table 41: Excluded Studies

Reference	Reason for exclusion
Lambert AS, Zhukouskaya V, Rothenbuhler A, Linglart A. X-linked hypophosphatemia: management and treatment prospects. Joint Bone Spine. 2019;31:31.	Review article
Insogna KL, Rauch F, Kamenicky P, et al. Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase III, single-arm, international trial. J Bone Miner Res. 2019;01:01. Ruppe MD, Zhang X, Imel EA, et al. Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia. Bone rep. 2016;5:158-162.	Study design

Appendix 3: Detailed Outcome Data

Table 42: RSS Total, Knee, and Wrist Scores in Study CL301

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
RSS total score		
Baseline – mean (SD)	3.17 (0.975)	3.19 (1.141)
Week 40[a,b] – mean (SD)	1.13 (0.715)	2.47 (1.092)
Change from baseline – LS mean (95% CI)	−2.04 (−2.33 to −1.75)	−0.71 (−0.98 to −0.43)
Difference (burosumab minus active control) (95% CI)	−1.34 (−1.74 to −0.94)	
P value	< 0.0001	
Proportion of patients achieving reduction from baseline at least 1.0,[c] n/N (%)	27/28 (96.4)	14/32 (43.8)
Proportion of patients who healed completely,[d] n/N (%)	0/28 (0)	0/32 (0)
Week 64[e] – mean (SD)	0.95 (0.724)	2.17 (0.947)
Change from baseline – LS mean (95% CI)	−2.23 (−2.46 to −2.00)	−1.01 (−1.31 to −0.72)
Difference (burosumab minus active control) (95% CI)	−1.21 (−1.59 to −0.83)	
P value	< 0.0001	
Proportion of patients achieving reduction from baseline at least 1.0,[c] n/N (%)	29/29 (100)	16/32 (50)
Proportion of patients who healed completely,[d] n/N (%)	4/29 (13.8)	0/32 (0)
RSS knee score		
Baseline – mean (SD)	1.69 (0.507)	1.73 (0.595)
Week 40[a,b] – mean (SD)	0.63 (0.376)	1.31 (0.504)
Change from baseline – LS mean (95% CI)	−1.10 (−1.26 to −0.93)	−0.41 (−0.56 to −0.25)
Difference (burosumab minus active control) (95% CI)	−0.69 (−0.91 to −0.46)	
P value	< 0.0001	
Week 64[e] – mean (SD)	0.60 (0.409)	1.19 (0.488)
Change from baseline – LS mean (95% CI)	−1.11 (−1.26 to −0.96)	−0.53 (−0.69 to −0.38)
Difference (burosumab minus active control) (95% CI)	−0.58 (−0.80 to −0.36)	
P value	< 0.0001	
RSS wrist score		
Baseline – mean (SD)	1.48 (0.661)	1.45 (0.807)
Week 40[a,b] – mean (SD)	0.48 (0.509)	1.16 (0.787)
Change from baseline – LS mean (95% CI)	−0.99 (−1.20 to −0.79)	−0.30 (−0.50 to −0.10)
Difference (burosumab minus active control) (95% CI)	−0.69 (−0.97 to −0.41)	
P value	< 0.0001	
Week 64[e] – mean (SD)	0.34 (0.519)	0.98 (0.701)
Change from baseline – LS mean (95% CI)	−1.13 (−1.29 to −0.97)	−0.49 (−0.68 to −0.29)

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Difference (burosumab minus active control) (95% CI)	−0.65 (−0.90 to −0.39)	
P value	< 0.0001	

ANCOVA = analysis of covariance; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; RSS = Rickets Severity Score; SD = standard deviation; SE = standard error.

[a] N = 28 at week 40 for the burosumab group for RSS total and knee scores.

[b] LS mean, SE, CI, and 2-sided P value per ANCOVA model, which included treatment group and baseline age stratification factor as independent variables and baseline RSS total score as a continuous covariate.

[c] Proportion is calculated among the patients who have a baseline RSS total score of at least 1.0.

[d] Proportion is calculated among the patients who have a baseline RSS total score > 0.

[e] LS mean, SE, CI, and 2-sided P value per GEE model, which included treatment, visit, treatment by visit interaction, and baseline age stratification factor as factors and baseline RSS total score as a continuous covariate.

Source: Clinical Study Report for Study CL301.[13]

Table 43: Subgroup Results for RSS Total in Study CL301

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Patients with baseline RSS total score > 2.5		
Baseline – n	18	20
Baseline – mean (SD)	3.61 (0.963)	3.78 (1.057)
Week 40		
Change from baseline – LS mean (95% CI)[a]	−2.47 (−2.75 to −2.19)	−1.11 (−1.51 to −0.72)
Difference (burosumab minus active control) (95% CI)	−1.36 (−1.85 to −0.87)	
P value	NR	
Proportion of patients achieving reduction from baseline of at least 1.0,[b] n/N (%)	18/18 (100)	12/20 (60)
Proportion of patients who healed completely,[c] n/N (%)	0/18 (0)	0/20 (0)
Week 64		
Change from baseline – LS mean (95% CI)[a]	−2.62 (−2.96 to −2.28)	−1.44 (−1.84 to −1.03)
Difference (burosumab minus active control) (95% CI)	−1.18 (−1.72 to −0.64)	
P value	NR	
Proportion of patients achieving reduction from baseline at least 1.0,[b] n/N (%)	19/19 (100)	14/20 (70)
Proportion of patients who healed completely,[c] n/N (%)	4/19 (21.1)	0/20 (0)
Patients with baseline RSS total score ≤ 2.5		
Baseline – n	10	12
Baseline – mean (SD)	2.35 (0.242)	2.21 (0.257)
Week 40		
Change from baseline – LS mean (95% CI)[a]	−1.37 (−1.60 to −1.14)	−0.05 (−0.49 to 0.40)
Difference (burosumab minus active control) (95% CI)	−1.32 (−1.84 to −0.80)	

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
P value	NR	
Proportion of patients achieving reduction from baseline at least 1.0,[b] n/N (%)	9/10 (90)	2/12 (16.7)
Proportion of patients who healed completely,[c] n/N (%)	0/10 (0)	0/12 (0)
Week 64		
Change from baseline – LS mean (95% CI)[a]	−1.52 (−1.74 to −1.29)	−0.30 (−0.59 to −0.01)
Difference (burosumab minus active control) (95% CI)	−1.22 (−1.59 to −0.85)	
P value		
Proportion of patients achieving reduction from baseline at least 1.0,[b] n/N (%)	10/10 (100)	2/12 (16.7)
Proportion of patients who healed completely,[c] n/N (%)	0/10 (0)	0/12 (0)
Patients with baseline age < 5		
Baseline – n	14	12
Baseline – mean (SD)	3.29 (1.139)	3.50 (1.477)
Week 40		
Change from baseline – LS mean (95% CI)[d]	−2.01 (−2.29 to −1.73)	−0.90 (−1.47 to −0.33)
Difference (burosumab minus active control) (95% CI)	−1.11 (−1.75 to −0.47)	
P value	NR	
Proportion of patients achieving reduction from baseline of at least 1.0,[b] n/N (%)	14/14 (100)	7/12 (58.3)
Proportion of patients who healed completely,[c] n/N (%)	0/14 (0)	0/12 (0)
Week 64		
Change from baseline – LS mean (95% CI)[d]	−2.26 (−2.50 to −2.02)	−1.40 (−1.94 to −0.86)
Difference (burosumab minus active control) (95% CI)	−0.86 (−1.45 to −0.27)	
P value	NR	
Proportion of patients achieving reduction from baseline of at least 1.0,[b] n/N (%)	14/14 (100)	8/12 (66.7)
Proportion of patients who healed completely,[c] n/N (%)	0/14 (0)	0/12 (0)
Patients with baseline age ≥ 5		
Baseline – n	14	20
Baseline – mean (SD)	3.04 (0.843)	3.00 (0.874)
Week 40		
Change from baseline – LS mean (95% CI)[d]	−2.16 (−2.41 to −1.90)	−0.59 (−0.95 to −0.23)
Difference (burosumab minus active control) (95% CI)	−1.57 (−2.00 to −1.13)	
P value	NR	
Proportion of patients achieving reduction from baseline of at least 1.0,[b] n/N (%)	13/14 (92.9)	7/20 (35.0)
Proportion of patients who healed completely,[c] n/N (%)	0/14 (0)	0/20 (0)

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Week 64		
Change from baseline – LS mean (95% CI)[d]	−2.20 (−2.56 to −1.84)	−0.76 (−1.07 to −0.45)
Difference (burosumab – active control) (95% CI)	−1.44 (−1.91 to −0.96)	
P value	NR	
Proportion of patients achieving reduction from baseline of at least 1.0,[b] n/N (%)	15/15 (100)	8/20 (40)
Proportion of patients who healed completely,[c] n/N (%)	4/15 (26.7)	0/20 (0)

CI = confidence interval; GEE = generalized estimating equation; LS = least squares; NR = not reported; RSS = Rickets Severity Score; SD = standard deviation; SE = standard error;

[a] GEE model includes treatment, visit, treatment by visit interaction, and baseline age stratification factor as factors and baseline RSS total score as continuous covariate. The LS mean, SE, and 95% CI are from the GEE.

[b] Proportion is calculated among the patients who have a baseline RSS total score of at least 1.0.

[c] Proportion is calculated among the patients who have a baseline RSS total score > 0.

[d] A GEE model includes treatment, visit, treatment by visit interaction, and baseline RSS total score as continuous covariate. The LS mean, SE, and 95% CI are from the GEE.

Source: Clinical Study Report for Study CL301.[13]

Table 44: Rickets Severity Scores and Change From Baseline in Studies CL201 and CL205

	Study CL201	Study CL205
	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
RSS wrist score		
Baseline, mean (SD)	0.71 (0.619)	1.27 (0.696)
Week 40, mean (SD)	0.17 (0.243)	0.50 (0.354)
Change to week 40, LS mean (95% CI)	−0.44 (−0.53 to −0.35)	−0.77 (−0.99 to −0.54)[b]
P value	< 0.0001[a]	< 0.0001[b]
Week 64, mean (SD)	0.31 (0.319)	NR
Change to week 40, LS mean (95% CI)	−0.30 (−0.42 to −0.19)	NR
P value	< 0.0001[a]	NR
RSS knee score		
Baseline, mean (SD)	1.21 (0.681)	1.65 (0.801)
Week 40, mean (SD)	0.58 (0.504)	0.69 (0.253)
Change to week 40, LS mean (95% CI)	−0.63 (−0.82 to −0.43)	−0.96 (−1.09 to −0.84)[b]
P value	< 0.0001[a]	< 0.0001[b]
Week 64, mean (SD)	0.50 (0.469)	NR
Change to week 40, LS mean (95% CI)	−0.70 (−0.87 to −0.53)	NR
P value	< 0.0001[a]	NR
RSS total score		
Baseline, mean (SD)	1.92 (1.172)	2.92 (1.367)
Week 40, mean (SD)	0.75 (0.552)	1.19 (0.522)
Change to week 40, LS mean (95% CI)	−1.06 (−1.28 to −0.85)	−1.73 (−2.03 to −1.44)[b]

	Study CL201	Study CL205
	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
P value	< 0.0001[a]	< 0.0001[b]
Week 64, mean (SD)	0.81 (0.601)	NR
Change to week 40, LS mean (95% CI)	−1.00 (−1.22 to −0.79)	NR
P value	< 0.0001[a]	NR
RSS responders at week 40 (n/m [%])[c] (ITT analysis set), n (%)		
All patients	16/20 (80.0)	NR
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	15/17(88.2)	NR
Lower RSS subgroup (baseline RSS total score < 1.5)	1/3 (33.3)	NR
RSS responders at week 64 (n/m [%])[c] (ITT analysis set), n (%)		
All patients	14/20 (70.0)	NR
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	14/17 (82.4)	NR
Lower RSS subgroup (baseline RSS total score < 1.5)	0/3 (0.0)	NR
Complete RSS responders at week 40 (n/m [%])[d] (ITT analysis set), n (%)		
All patients	6/25 (24.0)	NR
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	3/17 (17.6)	NR
Lower RSS subgroup (baseline RSS total score < 1.5)	3/8 (37.5)	NR
Complete RSS responders at week 64 (n/m [%])[d] (ITT analysis set), n (%)		
All patients	6/25 (24.0)	NR
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	2/17 (11.8)	NR
Lower RSS Subgroup (baseline RSS total score < 1.5)	4/8 (50.0)	NR

ANCOVA = analysis of covariance; CI = confidence interval; GEE = generalized estimating equation; ITT = intention to treat; LS = least squares; NR = not reported; LS = least squares; RSS = Rickets Severity Score; SD = standard deviation.

Note: RSS scores range from 0 to 4 for the wrist and from 0 to 6 for the knee, with higher scores associated with greater rickets severity. These scores are summed to generate an RSS total score.

[a] LS mean, P value, and CI per GEE model, which included visit, regimen, and visit by regimen as factors and RSS total score at baseline as covariate, with exchangeable covariance structure.

[b] LS mean, SE, 95% CI, and 2-sided P value from the ANCOVA model, which included age and RSS total score at baseline as covariates.

[c] Responders were defined as patients with a baseline RSS total score ≥ 1.0 (m) who had a reduction in RSS total score from baseline of at least 1.0 at the indicated time point (n).

[d] Complete RSS responders were defined as patients with a baseline RSS total score > 0 (m) and with an RSS total score = 0 at the indicated time point (n).

Source: Clinical study Reports for studies CL201 and CL205.[10,11]

Table 45: Radiographic Global Impression of Change Scores in Study CL301

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
RGI-C score[a]		
RGI-C global score (primary efficacy end point at week 40)		
Week 40[b] – LS mean (95% CI)	1.92 (1.70 to 2.14)	0.77 (0.56 to 0.99)
Difference (95% CI)	1.14 (0.83 to 1.45)	
P value	< 0.0001	
Week 64[c] – LS mean (95% CI)	2.06 (1.91 to 2.20)	1.03 (0.77 to 1.30)
Difference (95% CI)	1.02 (0.72 to 1.33)	
P value	< 0.0001	
RGI-C responders (RGI-C global scores ≥ +2.0)[d]		
Week 40, n (%)	21 (72.4)	2 (6.3)
Difference (burosumab minus active control)	66.2%	
Odds ratio (burosumab vs. active control) (95% CI)[e]	39.1 (7.2 to 211.7)	
P value	< 0.0001	
Week 64, n (%)	25 (86.2%)	6 (18.8%)
Difference (burosumab – active control), %	67.5%	
Odds ratio (burosumab vs. active control) (95% CI)[f]	34.1 (5.6 to 206.3)	
P value	0.0002	
RGI-C knee score		
Week 40[b] – LS mean (95% CI)	1.83 (1.62 to 2.04)	0.71 (0.51 to 0.91)
Difference (95% CI)	1.12 (0.84 to 1.41)	
P value	< 0.0001	
Week 64[c] – LS mean (95% CI)	2.03 (1.92 to 2.15)	1.03 (0.76 to 1.29)
Difference (95% CI)	1.01 (0.71 to 1.30)	
P value	< 0.0001	
RGI-C wrist score		
Week 40[b] – LS mean (95% CI)	2.07 (1.76 to 2.38)	0.76 (0.46 to 1.05)
Difference (95% CI)	1.31 (0.89 to 1.74)	
P value	< 0.0001	
Week 64[c] – LS mean (95% CI)	2.14 (1.91 to 2.36)	0.99 (0.71 to 1.26)
Difference (95% CI)	1.15 (0.78 to 1.51)	
P value	< 0.0001	
Lower limb deformity score		
Week 40[b] – LS mean (95% CI)	0.62 (0.37 to 0.87)	0.21 (−0.03 to 0.45)
Difference (95% CI)	0.41 (0.07 to 0.75)	
P value	0.0204	

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Week 64[c] – LS mean (95% CI)	1.25 (0.92 to 1.59)	0.29 (0.05 to 0.52)
Difference (95% CI)	0.97 (0.57 to 1.37)	
P value	< 0.0001	

ANCOVA = analysis of covariance; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SE = standard error; vs. = versus.

[a] The RGI-C score was based on a 7-point ordinal scale ranging from –3 (very much worse or severe worsening of rickets) to +3 (very much better or complete or near complete healing of rickets). The three radiologists were blinded to treatment assignment and patient data.

[b] LS mean, SE, CI, and 2-sided P value per ANCOVA model, which included RGI-C as the dependent variable; treatment group and baseline age stratification factor as independent variables; and baseline RSS total score as continuous covariate.

[c] LS mean, SE, CI, and 2-sided P value per GEE model, which included RGI-C as the dependent variable; treatment, visit, treatment by visit interaction, and baseline age stratification factor as factors; and baseline RSS total score as continuous covariate, with exchangeable covariate structure.

[d] RGI-C responder was defined as a patient with a mean RGI-C global score ≥ +2.0 at week 40. The RGI-C score was based on a 7-point ordinal scale ranging from –3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets). The three radiologists were blinded to treatment assignment and patient data.

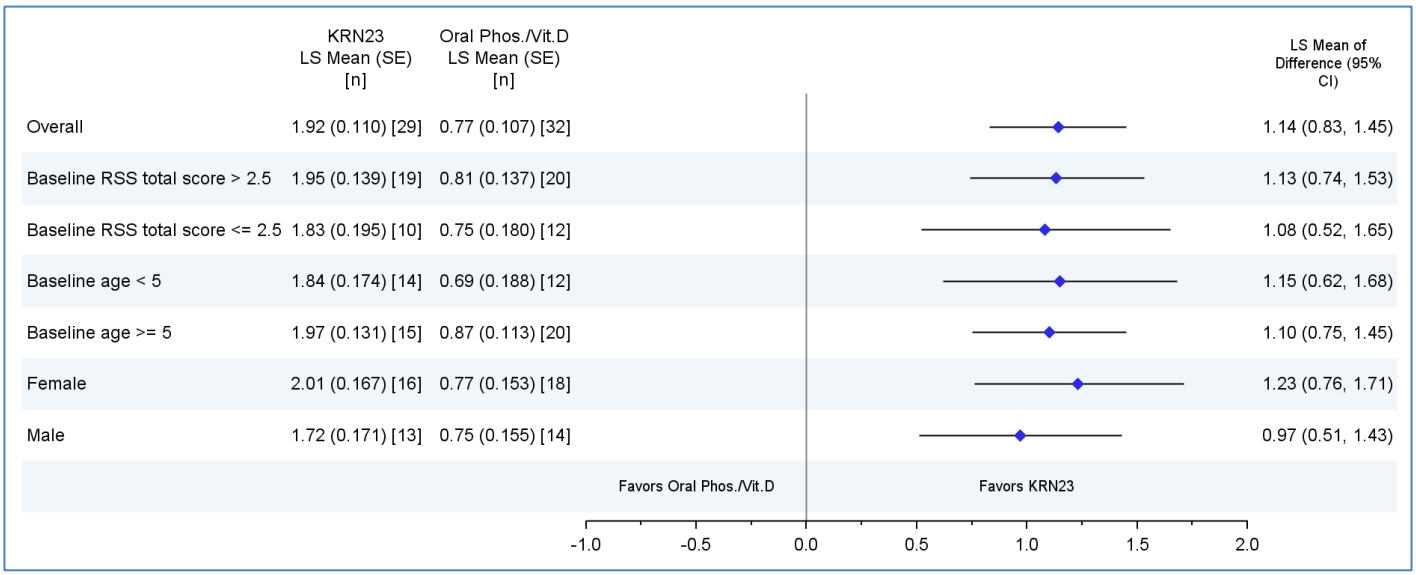
[e] Odds ratio, CI, and 2-sided P value were per logistic regression model, which included treatment group and baseline age stratification factor as independent variables and baseline RSS total score as continuous covariate.

[f] Odds ratio, CI, and 2-sided P value were per generalized linear mixed model, which includes treatment, visit, treatment by visit interaction, and baseline age stratification factor as factors, and baseline RSS total score as continuous covariate.

[g] The GEE model includes RGI-C as the dependent variable; treatment, visit, treatment by visit interaction, and baseline age stratification factor as factors; and baseline RSS total score as continuous covariate, with exchangeable covariate structure. The LS mean, SE, 95% CI, and 2-sided P value are from the GEE model.

Source: Clinical Study Report for Study CL301.[13]

Figure 2: RGI-C Global Scores Subgroup Analyses by Baseline RSS Total, Age, and Gender at Week 40 in Study CL301

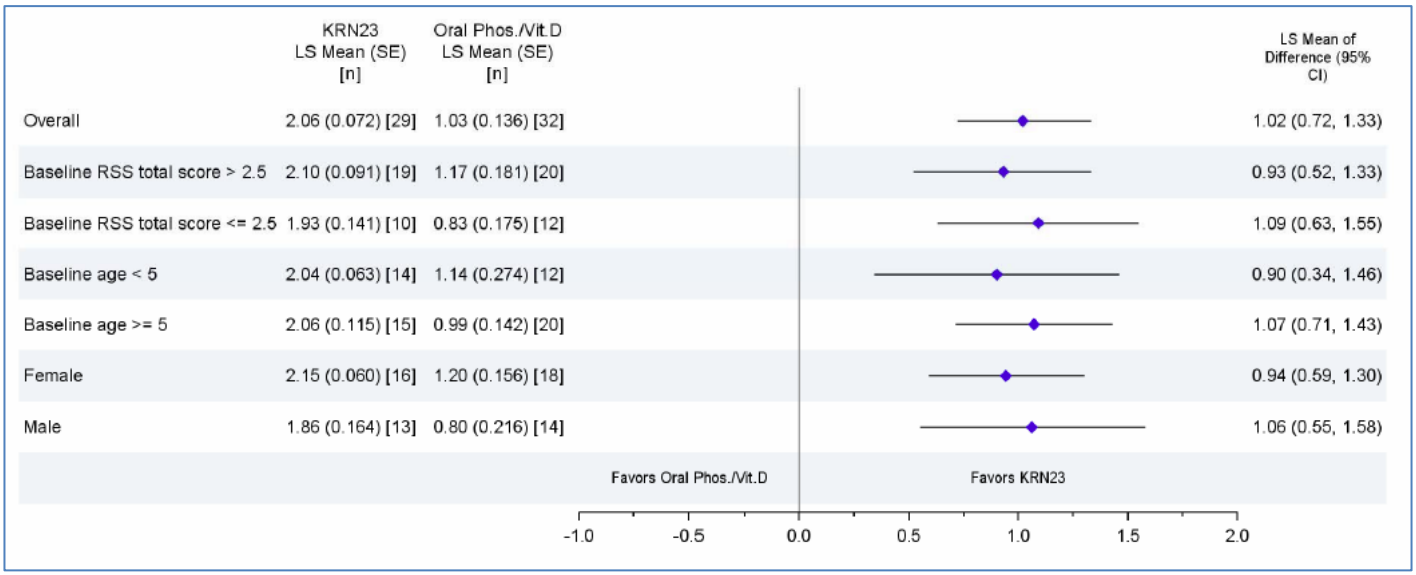


ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SE = standard error; Vit. D = vitamin D.

Note: LS mean, SE, CI, and 2-sided P value per ANCOVA model, which included RGI-C as the dependent variable; treatment group and baseline age stratification factor as independent variables; and baseline RSS total score as continuous covariate.

Source: Clinical Study Report for Study CL301.[13]

Figure 3: RGI-C Global Scores Subgroup Analyses by Baseline RSS Total, Age, and Gender at Week 40 in Study CL301



CI = confidence interval; GEE = generalized estimating equation; LS = least squares; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SE = standard error; Vit. D = vitamin D.

Note: The generalized GEE model includes RGI-C as the dependent variable; treatment, visit, treatment by visit interaction, and baseline age stratification factor as factors; and baseline RSS total score as continuous covariate, with exchangeable covariate structure. The LS mean, SE, and 95% CI are from the GEE model.

Source: Clinical Study Report for Study CL301.[13]

Table 46: RGI-C Scores and Change From Baseline in Studies CL201 and CL205

	Study CL201	Study CL205
	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
RGI-C wrist score		
At week 40, LS mean (95% CI)	+1.63 (1.35 to 1.92)	+2.26 (+2.01 to +2.50)[b]
P value	< 0.0001[a]	< 0.0001
At week 64, LS mean (95% CI)	+1.65 (1.35 to 1.95)	NR
P value	< 0.0001[a]	NR
RGI-C knee score		
At week 40, LS mean (95% CI)	+1.60 (1.39 to 1.80)	+2.21 (+1.86 to +2.55)[b]
P value	< 0.0001[a]	< 0.0001
At week 64, LS mean (95% CI)	+1.57 (1.37 to 1.77)	NR
P value	< 0.0001[a]	NR
RGI-C global score		
At week 40, LS mean (95% CI)	+1.66 (1.48 to 1.84)	+2.33 (+2.16 to +2.51)[b]
P value	< 0.0001[a]	< 0.0001
At week 64, LS mean (95% CI)	+1.56 (1.34 to 1.78)	NR

	Study CL201	Study CL205
	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
P value	< 0.0001[a]	NR
RGI-C lower limb deformity score		
At week 64 in CL201 and week 40 in CL205, LS mean (95% CI)	+0.59 (0.39 to 0.79)[c]	+1.26 (0.94 to 1.57)[b]
P value	< 0.0001	< 0.0001
Healing (RGI-C global score > +1.0), n (%)		
Week 40		
All patients	23/26 (88.5)	NR
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	17/17 (100)	NR
Lower RSS subgroup (baseline RSS total score < 1.5)	6/9 (66.7)	NR
Week 64		
All patients	21/26 (80.8)	NR
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	17/17 (100)	NR
Lower RSS subgroup (baseline RSS total score < 1.5)	4/9 (44.4)	NR
Substantial healing (RGI-C global score > +2.0), n (%)		
Week 40		
All patients	18/26 (69.2)	13 (100)
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	16/17 (94.1)	NR
Lower RSS subgroup (baseline RSS total score < 1.5)	2/9 (22.2)	NR
Week 64		
All patients	15/26 (57.7)	NR
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	14/17 (82.4)	NR
Lower RSS subgroup (baseline RSS total score < 1.5)	1/9 (11.1)	NR

ANCOVA = analysis of covariance; CI = confidence interval; GEE = generalized estimating equation; ITT = intention to treat; LS = least squares; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SE = standard error.

Note: The RGI-C score was based on a 7-point ordinal scale ranging from –3 (very much worse or severe worsening of rickets) to +3 (very much better or complete or near complete healing of rickets).

[a] LS mean and two-sided P value per GEE model, which included visit, regimen, and visit by regimen as factors, and RSS total score at baseline as covariate, with exchangeable covariance structure.

[b] LS mean, SE, 95% CI, and 2-sided P value from the ANCOVA model, which included age and RSS total score at baseline as covariates.

[c] LS mean, SE, and 2-sided P value are from the ANCOVA model, which included regimen group as factor and RSS at baseline as covariate.

Source: Clinical Study Reports for studies CL201 and CL205.[10,11]

Table 47: Standing Height and Growth Velocity of Standing Height in Study CL301

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Standing height or recumbent length z score		
Baseline – n	28	32
Mean (SD)	−2.32 (1.167)	−2.05 (0.868)
Week 40 – n	29	32
Mean (SD)	−2.12 (1.222)	−2.02 (0.849)
Change from baseline to week 40, LS mean (95% CI)[a]	+0.16 (0.05 to 0.26)	+0.03 (−0.03 to 0.10)
Difference (burosumab minus active control) (95% CI)[a]	+0.12 (+0.01 to +0.24)	
P value[a]	0.0408	
Week 64 – n	29	32
Mean (SD)	−2.11 (1.111)	−2.03 (0.829)
Change from baseline to week 64, LS mean (95% CI)[a]	+0.17 (0.04 to 0.30)	+0.02 (−0.04 to 0.09)
Difference (burosumab minus active control) (95% CI)[a]	+0.14 (+0.00 to +0.29)	
P value[a]	0.0490	
Standing height or recumbent length percentile for age and gender		
Baseline – n	28	32
Mean (SD)	5.87 (9.976)	5.74 (9.505)
Week 40 – n	29	32
Mean (SD)	8.35 (12.393)	5.43 (8.406)
Change from baseline to week 40 – n	28	32
Mean (SD)	+2.10 (4.060)	−0.30 (2.654)
Week 64 – n	29	32
Mean (SD)	7.61 (11.919)	5.06 (7.372)
Change from baseline to week 64 – n	28	32
Mean (SD)	+1.48 (6.364)	−0.68 (3.009)
Growth velocity[b] – z score		
Baseline[c] – n	22	22
Mean (SD)	−1.37 (1.334)	−0.96 (1.358)
Week 40[d] – n	22	22
Mean (SD)	+0.53 (1.796)	−0.37 (1.320)
Change from baseline to week 40, LS mean (95% CI)[e]	+1.76 (1.07 to 2.44)	+0.73 (0.05 to 1.42)
Difference (burosumab minus active control) (95% CI)[e]	+1.02 (+0.06 to +1.99)	
P value[e]	0.0386	
Week 64[d] – n	22	22
Mean (SD)	0.34 (1.458)	−0.75 (0.879)
Change from baseline to week 64, LS mean (95% CI)[e]	+1.53 (0.99 to 2.06)	+0.41 (−0.13 to 0.94)
Difference (burosumab minus active control) (95% CI)[e]	+1.12 (0.37 to 1.88)	
P value[e]	0.0047	
Growth velocity – cm/year		
Baseline[c] – n	26	26

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Mean (SD)	6.52 (4.035)	6.40 (2.386)
Week 40[d] – n	26	26
Mean (SD)	7.03 (2.050)	6.27 (1.314)
Change from baseline to week 40, mean (SD)	+0.51 (2.754)	−0.12 (2.092)
Week 64[d] – n	26	26
Mean (SD)	6.65 (1.459)	5.94 (1.116)
Change from baseline to week 64, mean (SD)	+0.13 (3.226)	−0.46 (1.989)

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; GEE = generalized estimating equation; SD = standard deviation; SE = standard error.

[a] LS mean, SE, CI, and 2-sided P value per GEE model, which included change from baseline for recumbent length or standing height z score as the dependent variable; treatment group, visit, interaction between treatment group by visit, and baseline RSS stratification as factors; and age and baseline recumbent length or standing height z score as continuous covariates, with exchangeable covariance structure. The P value is descriptive, as the primary analysis was at week 64.

[b] Growth velocity z score was calculated for patients age ≥ 2.25 years.

[c] Baseline growth velocity was calculated based on the standing height measured within 1.5 years prior to baseline.

[d] Patients with baseline growth velocity.

[e] LS mean, SE, CI, and 2-sided P value per ANCOVA model, which included change from baseline for growth velocity z score as the dependent variable; treatment group and baseline RSS total score stratification as factors; and baseline z score and age as continuous covariates. The P value is descriptive, given that the primary analysis was at week 64.

Source: Clinical Study Report for Study CL301.[13]

Table 48: Growth Velocity (cm/year) at Baseline and Week 64 Based on Standing Height (ITT Analysis Set) in Study CL201

	Study CL201
	Burosumab every two weeks (N = 26)
Growth velocity[a]	
All patients	
n	25
Baseline[b] (cm/year), mean (SD)	5.45 (1.171)
Week 64 (cm/year), mean (SD)	6.14 (1.466)
Change to week 64. mean (SD)	+0.73 (1.399)
P value[c]	0.0160
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	
n	17
Baseline[b] (cm/year), mean (SD)	5.05 (1.036)
Week 64 (cm/year), mean (SD)	6.16 (1.772)
Change to week 64. mean (SD)	+1.11 (1.496)
P value[c]	0.0076
Lower RSS subgroup (baseline RSS total score < 1.5)	
n	8
Baseline[b] (cm/year), mean (SD)	6.30 (1.018)
Week 64 (cm/year), mean (SD)	6.12 (0.656)

	Study CL201
	Burosumab every two weeks (N = 26)
Change to week 64, mean (SD)	−0.09 (0.698)
P value[c]	0.7350

CI = confidence interval. ITT = intention to treat; RSS = Rickets Severity Score; SD = standard deviation.

[a] Data presented for patients with evaluable growth velocity data at baseline. Baseline growth velocity was calculated based on the standing height measured within 2 years prior to baseline.

[b] Growth velocity could not be calculated for one patient for whom pre-treatment height data were not available.

[c] The one-sample t-test was used for P value and 95% CI on growth velocity (cm/year) change from baseline.

Source: Clinical Study Report for Study CL201.[10]

Table 49: Standing Height Z Score and Standing Height Percentile (ITT Analysis Set) in Study CL201

	Study CL201
	Burosumab every two weeks (N = 26)
Standing height (z score)	
All patients	
n	26
Baseline, mean (SD)	−1.72 (1.026)
Week 64, mean (SD)	−1.54 (1.127)
Change to week 64, LS mean (95% CI)[a]	+0.19 (0.09 to 0.29)
P value	0.0002
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	
n	17
Baseline, mean (SD)	−2.14 (0.924)
Week 64, mean (SD)	−1.96 (1.082)
Change to week 64, LS mean (95% CI)[a]	+0.19 (0.05 to 0.32)
P value	0.0063
Lower RSS subgroup (baseline RSS total score < 1.5)	
n	9
Baseline, mean (SD)	−0.93 (0.711)
Week 64, mean (SD)	−0.75 (0.746)
Change to week 64, LS mean (95% CI)[a]	+0.19 (0.07 to 0.31)
P value	0.0017
Standing height percentile	
All patients	
n	26
Baseline, mean (SD)	11.13 (13.798)
Week 64, mean (SD)	15.04 (17.443)
Change to week 64, mean (SD)	+3.91 (4.893)
Higher RSS subgroup (baseline RSS total score ≥ 1.5)	
n	17

	Study CL201
	Burosumab every two weeks (N = 26)
Baseline, mean (SD)	5.22 (8.382)
Week 64, mean (SD)	8.41 (12.924)
Change to week 64, mean (SD)	+3.19 (4.891)
Lower RSS subgroup (baseline RSS total score < 1.5)	
n	9
Baseline, mean (SD)	22.30 (15.485)
Week 64, mean (SD)	27.58 (18.614)
Change to week 64, mean (SD)	+5.28 (4.875)

CI = confidence interval; GEE = generalized estimating equation; ITT = intention to treat; LS = least squares; RSS = Rickets Severity Score; SD = standard deviation; SE = standard error.

[a] The GEE model included change from baseline for standing height z score as the dependent variable; visit, regimen, visit by regimen, and gender as factors; and age and standing height z score at baseline as covariates, with exchangeable covariance structure. The LS mean, SE, 95% CI, and two-sided P value were from the GEE model.

Source: Clinical Study Report for Study CL201.[10]

Table 50: Recumbent Length or Standing Height at Baseline and Week 40 (Efficacy Analysis Set) in Study CL205

	Study CL205
	Burosumab every two weeks (N = 13)
Recumbent length or standing height	
Recumbent length or standing height (cm)	
Baseline	
Mean (SD)	89.15 (7.597)
Median (range)	90.20 (77.5 to 101.5)
Week 40	
Mean (SD)	93.44 (7.045)
Median (range)	94.10 (81.6 to 105.3)
Change from baseline to week 40	
Mean (SD)	4.29 (2.451)
Median (range)	4.10 (0.1 to 9.4)
Recumbent length or standing height (percentile)	
Baseline	
Mean (SD)	18.044 (25.2644)
Median (range)	8.519 (0.01 to 83.29)
Week 40	
Mean (SD)	12.761 (18.9433)
Median (range)	5.358 (0.00 to 62.07)
Change from baseline to week 40	
Mean (SD)	−5.283 (20.1675)
Median (range)	−0.281 (−70.42 to 9.82)
Recumbent length/standing height (z score)	

	Study CL205
	Burosumab every two weeks (N = 13)
Baseline	
Mean (SD)	−1.378(1.1947)
Median (range)	−1.371 (−3.66 to 0.97)
Week 40	
Mean (SD)	−1.654 (1.1195)
Median (range)	−1.611 (−4.03 to 0.31)
Change from baseline to week 40	
Mean (SD)	−0.276 (0.6647)
Median (range)	−0.183 (−2.10 to 0.29)
Change to week 40. LS mean (95% CI)[a]	−0.20 (−0.46 to 0.06)
P value	0.1396

CI = confidence interval; GEE = generalized estimating equation; LS = least squares; SD = standard deviation; SE = standard error.

[a] LS mean, SE, 95% CI, and 2-sided P value from the GEE model, which included visit and gender as factors and age and standing height z score at baseline as covariates, with exchangeable covariance structure.

Source: Clinical Study Report for Study CL205.[11]

Table 51: Serum Phosphorus Concentration, Alkaline Phosphatase, TmP/GFR, TRP, and 1,25-Dihydroxyvitamin D in Study CL301

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Alkaline phosphatase (U/L)		
n	29	32
Baseline, mean (SD)	510.76 (124.903)	523.44 (154.419)
Week 40, mean (SD)	380.76 (99.464)	488.69 (189.070)
Change from baseline, LS mean (95% CI)[a]	−130.72 (−154.96 to −106.49)	−34.78 (−70.31 to 0.76)
Difference (burosumab minus active control) (95% CI)	−95.95 (−136.05 to −55.84)	
P value	< 0.0001	
Week 64, mean (SD)	336.86 (86.126)	495.41 (182.065)
Change from baseline, LS mean (95% CI)[a]	−174.62 (−200.94 to −148.30)	−28.06 (−67.22 to 11.10)
Difference (burosumab – active control) (95% CI)	−146.56 (−191.61 to −101.52)	
P value	< 0.0001	
Serum phosphorus concentration (mmol/L)		
n	29	32
Baseline, mean (SD)	0.78 (0.077)	0.74 (0.082)
Week 40, mean (SD)	1.09 (0.120)	0.82 (0.093)
LS mean change from baseline (95% CI) to week 40[b]	0.32 (0.28 to 0.36)	0.07 (0.03 to 0.11)
Difference (burosumab – active control) (95% CI)	0.25 (0.20 to 0.30)	
P value	< 0.0001	
Week 64, mean (SD)	1.08 (0.117)	0.83 (0.096)

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
LS mean change from baseline (95% CI) to week 64[c]	0.31 (0.28 to 0.35)	0.07 (0.04 to 0.11)
Difference (burosumab – active control) (95% CI)	0.24 (0.19 to 0.29)	
P value	< 0.0001	
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40, n (%)	17 (58.6)	1 (3.1)
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 64, n (%)	19 (65.5)	1 (3.1)
Change from baseline in serum phosphorus level ≥ 0.16 mmol/L at week 40, n (%)	24 (82.8)	7 (21.9)
Change from baseline in serum phosphorus level ≥ 0.16 mmol/L at week 64, n (%)	25 (86.2)	8 (25.0)
Change from baseline in serum phosphorus level ≥ 0.22 mmol/L at week 40, n (%)	19 (65.5)	4 (12.5)
Change from baseline in serum phosphorus level ≥ 0.22 mmol/L at week 64, n (%)	19 (65.5)	3 (9.4)
Change from baseline in serum phosphorus level ≥ 0.32 mmol/L at week 40, n (%)	12 (41.4)	2 (6.3)
Change from baseline in serum phosphorus level ≥ 0.32 mmol/L at week 64, n (%)	10 (34.5)	1 (3.1)
TmP/GFR (mmol)		
Baseline, n	24	30
Mean (SD)	0.71 (0.121)	0.65 (0.107)
Week 40, n	28	30
Mean (SD)	1.08 (0.215)	0.59 (0.113)
LS mean change from baseline (95% CI) to week 40[d]	0.39 (0.32 to 0.46)	−0.05 (−0.08 to −0.02)
Difference (burosumab – active control) (95% CI)	0.44 (0.36 to 0.52)	
P value	< 0.0001	
Week 64, n	26	32
Mean (SD)	1.06 (0.209)	0.61 (0.159)
LS mean change from baseline (95% CI) to week 64[d]	0.37 (0.29 to 0.45)	−0.03 (−0.07 to 0.01)
Difference (burosumab – active control) (95% CI)	0.40 (0.31 to 0.50)	
P value	< 0.0001	
Patients reaching the normal range (0.84 - 1.42 mmol/L) at week 40, n (%)	23 (82.1)	1 (3.3)
Patients reaching the normal range (0.84 - 1.42 mmol/L) at week 64, n (%)	21 (80.8)	1 (3.1)
TRP		
Baseline, n	24	30
Mean (SD)	0.86 (0.065)	0.85 (0.080)
Week 40, n	28	30
Mean (SD)	0.90 (0.047)	0.72 (0.109)
LS mean change from baseline (95% CI) to week 40[e]	0.05 (0.03 to 0.07)	−0.12 (−0.16 to −0.08)
Difference (burosumab – active control) (95% CI)	0.17 (0.13 to 0.21)	

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
P value	< 0.0001	
Week 64, n	26	32
Mean (SD)	0.90 (0.048)	0.73 (0.132)
LS mean change from baseline (95% CI) to week 64[e]	0.04 (0.02 to 0.06)	−0.11 (−0.15 to −0.06)
Difference (burosumab – active control) (95% CI)	0.15 (0.10 to 0.20)	
P value	< 0.0001	
1,25-dihydroxyvitamin D (pmol/L)		
Baseline, n	28	30
Mean (SD)	110.36 (48.106)	96.42 (35.729)
Week 40, n	26	29
Mean (SD)	174.17 (51.208)	142.23 (46.764)
LS mean change from baseline (95% CI) to week 40[f]	71.07 (53.57 to 88.56)	44.19 (27.29 to 61.09)
Difference (burosumab – active control) (95% CI)	26.88 (2.34 to 51.42)	
P value	0.0318	
Week 64, n	28	31
Mean (SD)	129.81 (31.072)	105.78 (32.770)
LS mean change from baseline (95% CI) to week 64[f]	23.76 (13.25 to 34.27)	2.85 (−10.24 to 15.95)
Difference (burosumab – active control) (95% CI)	20.91 (4.17 to 37.65)	
P value	0.0144	

ALP = alkaline phosphatase; ANCOVA = analysis of covariance; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; SD = standard deviation; SE= standard error; TmP/GFR = ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate; TRP = tubular reabsorption of phosphate.

[a] The generalized GEE model includes change from baseline for ALP measurement as the dependent variable; treatment group, visit, interaction between treatment group by visit, baseline age, and baseline RSS stratification as factors; and baseline ALP measure as covariate, with exchangeable covariance structure. The LS mean, SE, 95% CI, and 2-sided P value are from the GEE model.

[b] The ANCOVA model includes change in serum phosphorus from baseline to mean post-baseline as the dependent variable; treatment group, baseline age, and baseline RSS stratification as factors; and baseline phosphorus measure as covariate.

[c] The GEE model includes change from baseline for serum phosphorous measurement as the dependent variable; treatment group, visit, interaction between treatment group by visit, baseline age, and baseline RSS stratification as factors; and baseline phosphorous measure as covariate, with exchangeable covariance structure. The LS mean, SE, 95% CI, and 2-sided P value are from the GEE model.

[d] The GEE model includes change from baseline for TmP/GFR measurement as the dependent variable; treatment group, visit, interaction between treatment group by visit, baseline age, and baseline RSS stratification as factors; and baseline TmP/GFR measure as covariate, with exchangeable covariance structure. The LS mean, SE, 95% CI, and 2-sided P value are from the GEE model.

[e] The GEE model includes change from baseline for TRP measurement as the dependent variable; treatment group, visit, interaction between treatment group by visit, baseline age, and baseline RSS stratification as factors; and baseline TRP measure as covariate, with exchangeable covariance structure. The LS mean, SE, 95% CI, and 2-sided P value are from the GEE model.

[f] The GEE model includes change from baseline for 1,25-dihydroxyvitamin D measurement as the dependent variable; treatment group, visit, interaction between treatment group by visit, baseline age, and baseline RSS stratification as factors; and baseline 1,25-dihydroxyvitamin D measure as covariate, with exchangeable covariance structure. The LS mean, SE, 95% CI, and 2-sided P value are from the GEE model.

Source: Clinical Study Report for Study CL301.[13]

Table 52: Subgroup Results for Serum Phosphorus Concentration in Study CL301

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Serum phosphorus concentration (mmol/L)		
Patients with baseline RSS total score > 2.5		
Baseline, n	19	20
Baseline, mean (SD)	0.78 (0.071)	0.74 (0.095)
Week 40, mean (SD)	1.02 (0.125)	0.83 (0.108)
LS mean change from baseline (95% CI) to week 40[a]	0.25 (0.20 to 0.29)	0.08 (0.03 to 0.13)
Difference (burosumab – active control) (95% CI)	0.16 (0.09 to 0.24)	
P value	NR	
Week 64, mean (SD)	1.05 (0.140)	0.82 (0.145)
LS mean change from baseline (95% CI) to week 64[a]	0.27 (0.21 to 0.33)	0.07 (0.01 to 0.13)
Difference (burosumab – active control) (95% CI)	0.20 (0.12 to 0.29)	
P value	NR	
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40, n (%)	9 (47.4)	1 (5.0)
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 64, n (%)	11 (57.9)	1 (5.0)
Patients with baseline RSS total score ≤ 2.5		
Baseline, n	10	12
Baseline, mean (SD)	0.80 (0.091)	0.75 (0.059)
Week 40, mean (SD)	1.16 (0.115)	0.79 (0.114)
LS mean change from baseline (95% CI) to week 40[a]	0.38 (0.30 to 0.46)	0.03 (−0.03 to 0.09)
Difference (burosumab – active control) (95% CI)	0.35 (0.24 to 0.46)	
P value	NR	
Week 64, mean (SD)	1.10 (0.126)	0.82 (0.091)
LS mean change from baseline (95% CI) to week 64[a]	0.32 (0.25 to 0.39)	0.06 (0.01 to 0.11)
Difference (burosumab – active control) (95% CI)	0.26 (0.16 to 0.36)	
P value	NR	
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40, n (%)	8 (80.0)	0 (0.0)
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 64, n (%)	8 (80.0)	0 (0.0)
Patients with baseline age < 5		
Baseline, n	14	12
Baseline, mean (SD)	0.82 (0.071)	0.77 (0.069)
Week 40, mean (SD)	1.07 (0.153)	0.82 (0.107)
LS mean change from baseline (95% CI) to week 40[b]	0.26 (0.20 to 0.31)	0.06 (0.01 to 0.12)
Difference (burosumab – active control) (95% CI)	0.20 (0.12 to 0.27)	
P value	NR	
Week 64, mean (SD)	1.06 (0.115)	0.84 (0.156)
LS mean change from baseline (95% CI) to week 64[b]	0.25 (0.21 to 0.29)	0.08 (0.00 to 0.16)

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Difference (burosumab – active control) (95% CI)	0.17 (0.08 to 0.26)	
P value	NR	
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40, n (%)	9 (64.3)	0 (0.0)
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 64, n (%)	9 (64.3)	1 (8.3)
Patients with baseline age ≥ 5		
Baseline, n	15	20
Baseline, mean (SD)	0.75 (0.069)	0.73 (0.087)
Week 40, mean (SD)	1.06 (0.127)	0.81 (0.116)
LS mean change from baseline (95% CI) to week 40[b]	0.32 (0.25 to 0.39)	0.08 (0.02 to 0.13)
Difference (burosumab – active control) (95% CI)	0.24 (0.16 to 0.33)	
P value	NR	
Week 64, mean (SD)	1.06 (0.156)	0.81 (0.107)
LS mean change from baseline (95% CI) to week 64[b]	0.32 (0.24 to 0.40)	0.07 (0.03 to 0.11)
Difference (burosumab – active control) (95% CI)	0.25 (0.16 to 0.34)	
P value	NR	
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 40, n (%)	8 (53.3)	1 (5.0)
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L) at week 64, n (%)	10 (66.7)	0 (0.0)

CI = confidence interval; GEE = generalized estimating equation; LS = least squares; NR = not reported; RSS = Rickets Severity Score; SD = standard deviation; SE = standard error; TmP/GFR = ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate; TRP = tubular reabsorption of phosphate.

[a] The GEE model includes change from baseline for serum phosphorous measurement as the dependent variable; treatment group, visit, interaction between treatment group by visit, baseline age; and baseline RSS stratification as factors; and baseline phosphorous measure as covariate, with exchangeable covariance structure. The LS mean, SE, and 95% CI are from the GEE model.

[b] The GEE model includes change from baseline for serum phosphorous measurement as the dependent variable; treatment group, visit, interaction between treatment group by visit, and baseline RSS stratification as factors; and baseline phosphorous measure as covariate, with exchangeable covariance structure. The LS mean, SE, and 95% CI are from the GEE model.

Source: Clinical Study Report for Study CL301.[13]

Table 53: ALP, Serum Phosphorus Concentration, TmP/GFR, TRP, 1,25(OH)$_2$D, and BALP in Studies CL201 and CL205

	Study CL201	Study CL205
	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
Serum phosphorus level (mmol/L)		
Baseline, mean (SD)	0.77 (0.131)	0.810 (0.0918)
Week 40, n	26	13
Week 40, mean (SD)	1.07 (0.128)	1.122 (0.1579)
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L), n (%)	17 (65.4)	10 (76.9)
Change from baseline in serum phosphorus level ≥ 0.16 mmol/L, n (%)	23 (88.5)	12 (92.3)
Change from baseline in serum phosphorus level ≥ 0.22 mmol/L, n (%)	NR	10 (76.9)

	Study CL201	Study CL205
	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
Change from baseline in serum phosphorus level ≥ 0.32 mmol/L, n (%)	11 (42.3)	6 (46.2)
LS mean change from baseline (95% CI) to week 40	NR	0.31 (0.24 to 0.39)[a]
P value	NR	< 0.0001
Week 64, n	24	NR
Week 64, mean (SD)	1.08 (0.144)	NR
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L), n (%)	16 (66.7)	NR
Change from baseline in serum phosphorus level ≥ 0.16 mmol/L, n (%)	21 (87.5)	NR
Change from baseline in serum phosphorus level ≥ 0.32 mmol/L, n (%)	12 (50.0)	NR
Subgroup of patients with baseline RSS total score ≥ 1.5		
Week 40, n	17	NR
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L), n (%)	9 (52.9)	NR
Change from baseline in serum phosphorus level ≥ 0.16 mmol/L, n (%)	16 (94.1)	NR
Change from baseline in serum phosphorus level ≥ 0.32 mmol/L, n (%)	9 (52.9)	NR
Week 64, n	16	NR
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L), n (%)	10 (62.5)	NR
Change from baseline in serum phosphorus level ≥ 0.16 mmol/L, n (%)	14 (87.5)	NR
Change from baseline in serum phosphorus level ≥ 0.32 mmol/L, n (%)	10 (62.5)	NR
Subgroup of patients with baseline RSS total score < 1.5		
Week 40, n	9	NR
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L), n (%)	8 (88.9)	NR
Change from baseline in serum phosphorus level ≥ 0.16 mmol/L, n (%)	7 (77.8)	NR
Change from baseline in serum phosphorus level ≥ 0.32 mmol/L, n (%)	2 (22.2)	NR
Week 64, n	8	NR
Patients reaching the normal range (1.03 mmol/L to 1.97 mmol/L), n (%)	6 (75.0)	NR
Change from baseline in serum phosphorus level ≥ 0.16 mmol/L, n (%)	7 (87.5)	NR
Change from baseline in serum phosphorus level ≥ 0.32 mmol/L, n (%)	2 (25.0)	NR
TmP/GFR (mmol/L)		
Baseline, n	25	NR
Baseline, mean (SD)	0.70 (0.159)	NR
Week 40, n	1.07 (0.195)	NR
Week 40, mean (SD)	25	NR
Patients reaching the normal range (0.84 mmol/L to 1.42 mmol/L), n (%)	21 (84.0)	NR
Week 64, n	1.08 (0.171)	NR
Week 64, mean (SD)	21	NR
Patients reaching the normal range (0.84 mmol/L to 1.42 mmol/L), n (%)	19 (90.5)	NR
TRP		
Baseline, mean (SD)	0.86 (0.067)	NR
Week 40, mean (SD)	0.90 (0.040)	NR
Week 64, mean (SD)	0.91 (0.023)	NR

	Study CL201	Study CL205
	Burosumab every two weeks (N = 26)	Burosumab every two weeks (N = 13)
1,25(OH)2D (pmol/L)		
Baseline, mean (SD)	107.34 (57.115)	116.58 (45.811)
Week 40, mean (SD)	180.85 (39.373)	136.18 (24.825)
LS mean change from baseline (95% CI) to week 40	NR	19.38 (3.37 to 35.39)[a]
P value	NR	0.0177
Week 64, mean (SD)	168.65 (42.532)	NR
Alkaline phosphatase (U/L)		
Baseline, mean (SD)	461.9 (110.21)	548.5 (193.80)
Week 40, mean (SD)	382.5 (88.03)	335.4 (87.59)
LS mean change from baseline (95% CI) to week 40	NR	−213.08 (−239.59 to −186.56)[a]
P value	NR	< 0.0001
Week 64, mean (SD)	354.2 (73.37)	NR
Bone-specific alkaline phosphatase (ug/L)		
Baseline, mean (SD)	163.54 (58.610)	NR
Week 40, mean (SD)	130.04 (38.923)	NR
Week 64, mean (SD)	110.06 (31.194)	NR

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; ALP = alkaline phosphate; BALP = bone-specific alkaline phosphatase; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; NR = not reported; SE = standard error; TmP/GFR = ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate; TRP = tubular reabsorption of phosphate.

[a] The GEE model includes change from baseline as the dependent variable; time as the categorical variable and adjusted for baseline measurement, with exchangeable covariance structure. The LS, SE, 95% CI, and 2-sided P values are from the GEE model.

Source: Clinical Study Reports for studies CL201 and CL205.[10,11]

Table 54: Rickets, Serum Phosphorus, and Standing Height Z Score to Week 64 by Age Subgroups (ITT Analysis Set) in Study CL201

	Study CL201			
	Burosumab every two weeks (N = 26)			
	RSS total score[a]	RGI-C global score[a]	Serum phosphorus (mg/dL)[b]	Standing height z score[c]
Age 5 years to < 9 years				
n	10	10	10	9
Baseline, mean (SD)	1.40 (1.022)	[d]	2.65 (0.477)	−1.47 (1.217)
Week 40, mean (SD)	0.70 (0.537)	1.73 (0.540)	3.38 (0.391)	−1.26 (1.157)
Change to week 40, LS mean (SE)	–0.93 (0.159)	[d]	0.73 (0.566)[e]	0.20 (0.044)
P value	< 0.0001	< 0.0001	0.0028	< 0.0001
Patients reaching the normal range of serum phosphorus level (3.2 mg/dL to 6.1 mg/dL) at	NA	NA	7/10 (70.0)	NA

	Study CL201			
	Burosumab every two weeks (N = 26)			
	RSS total score[a]	RGI-C global score[a]	Serum phosphorus (mg/dL)[b]	Standing height z score[c]
week 40, n/N (%)				
Week 64, mean (SD)	0.85 (0.626)	1.47 (0.773)	3.44 (0.447)	−1.30 (1.176)
Change to week 64, LS mean (SE)	−0.78 (0.151)	[d]	0.78 (0.609)[e]	0.27 (0.041)
P value	< 0.0001	< 0.0001	0.0087	< 0.0001
Patients reaching the normal range of serum phosphorus level (3.2 mg/dL to 6.1 mg/dL) at week 64, n/N (%)	NA	NA	6/8 (75.0)	NA
Age 9 years to 12 years				
n	16	16	16	15
Baseline, mean (SD)	2.25 (1.169)	[d]	2.21 (0.238)	−1.67 (0.768)
Week 40, mean (SD)	0.78 (0.576)	1.71 (0.643)	3.25 (0.403)	−1.53 (0.771)
Change to week 40, LS mean (SE)	−1.09 (0.148)	[d]	1.04 (0.390)[e]	0.13 (0.055)
P value	< 0.0001	< 0.0001	< 0.0001	0.0173
Patients reaching the normal range of serum phosphorus level (3.2 mg/dL to 6.1 mg/dL) at week 40, n/N (%)	NA	NA	10 (62.5)	NA
Week 64, mean (SD)	0.78 (0.605)	1.71 (0.842)	3.30 (0.452)	−1.69 (1.108)
Change to week 64, LS mean (SE)	−1.09 (0.147)	[d]	1.09 (0.422)[e]	0.12 (0.066)
P value	< 0.0001	< 0.0001	< 0.0001	0.0654
Patients reaching the normal range of serum phosphorus level (3.2 mg/dL to 6.1 mg/dL) at week 64, n/N (%)	NA	NA	10 (62.5)	NA

CI = confidence interval; GEE = generalized estimating equation; ITT = intention to treat; LS = least squares; NA = not applicable; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SD = standard deviation; SE = standard error.

[a] P value per GEE model, which included visit, regimen, and visit by regimen as factors, and RSS total score at baseline as covariate, with exchangeable covariance structure.

[b] P values for change from baseline were calculated using the one-sample t-test.

[c] The GEE model includes change from baseline for standing height z score as the dependent variable; visit, regimen, visit by regimen, and gender as factors; and age and standing height z score at baseline as covariates, with exchangeable covariance structure. The LS mean, SE, 95% CI, and 2-sided P value are from the GEE model.

[d] The RGI-C score represents a change from a previous radiograph; the method does not include a baseline value.

[e] Mean (SD).

Source: Clinical Study Report for Study CL201.[10]

Table 55: Proportion of Patients Achieving Mean Serum Phosphorus Levels Above the LLN in Study CL303

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Achieved mean serum phosphorus > LLN across midpoints of dose intervals through week 24 – n (%)	64 (94.1)	5 (7.6)
95% CI[a]	(85.8 to 97.7)	(3.3 to 16.5)
P value[b]	< 0.0001	
Subgroup of patients with baseline BPI worst pain ≤ 6.0	45 (93.8)	4 (8.2)
95% CI[a]	(83.2 to 97.9)	(3.2 to 19.2)
Subgroup of patients with baseline BPI worst pain > 6.0	19 (95.0)	1 (5.9)
95% CI[a]	(76.4 to 99.1)	(1.0 to 27.0)

BPI = Brief Pain Inventory; CI = confidence interval; LLN = lower limit of normal.

[a] The 95% CIs for the proportion of patients who achieve mean serum phosphorus levels above the LLN were calculated using the Wilson score method.

[b] The P value is from Cochran-Mantel-Haenszel testing for association between achieving mean serum phosphorus levels above the LLN and treatment group, adjusting for the actual randomization stratification of BPI average pain and region.

Source: Clinical Study Report for Study CL303.[12]

Table 56: Change From Baseline in Serum $1,25(OH)_2D$, TmP/GFR, TRP, and BALP in Study CL303

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Serum $1,25(OH)_2D$ pg/mL		
Baseline, n	66	64
Mean (SD)	32.4 (12.96)	33.5 (15.61)
Range	4, 76	4, 80
At week 22, n	67	66
Mean (SD)	57.0 (18.02)	34.9 (14.52)
LS mean (95% CI) change from baseline	25.85 (19.23 to 32.47)	3.12 (−2.04 to 8.29)
LS mean (95% CI) difference (burosumab minus placebo)	22.73 (18.08 to 27.38)	
P value	< 0.0001	
TmP/GFR mg/dL		
Baseline, n	66	64
Mean (SD)	1.68 (0.400)	1.60 (0.369)
Range	1.0 to 3.4	0.7 to 2.6
Week 24, n	68	64
Mean (SD)	2.21 (0.488)	1.73 (0.424)
LS mean (95% CI) change from baseline	0.56 (0.36 to 0.76)	0.13 (−0.03 to 0.29)
LS mean (95% CI) difference (burosumab minus placebo)	0.43 (0.30 to 0.57)	
P value	< 0.0001	

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
TRP		
Baseline, n	67	64
Mean (SD)	0.81 (0.083)	0.81 (0.084)
Range	0.6 to 1.0	0.5 to 0.9
Week 24, n	68	65
Mean (SD)	0.84 (0.065)	0.80 (0.106)
LS mean (95% CI) change from baseline	0.03 (0.01 to 0.05)	−0.01 (−0.04 to 0.01)
LS mean (95% CI) difference (burosumab – placebo)	0.04 (0.02 to 0.07)	
P value	0.0008	
BALP mcg/L		
Baseline, n	65	66
Mean (SD)	24.0 (19.68)	24.7 (17.25)
Week 24, n	66	61
Mean (SD)	30.2 (26.26)	26.0 (17.33)
LS mean (95% CI) change from baseline	5.14 (1.04 to 9.24)	1.08 (−2.87 to 5.03)
LS mean (95% CI) difference (burosumab – placebo)	4.06 (−0.75 to 8.87)	
P value	0.0983	

1,25$(OH)_2$D = 1,25-dihydroxyvitamin D; BALP = bone-specific alkaline phosphatase; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; SD = standard deviation; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; TRP = tubular reabsorption rate of phosphate.

Note: The LS mean estimates and P values are from the GEE model, which includes the change (or percentage change) from baseline as the dependent variable; region, visit, treatment, actual randomization stratification, and visit by treatment as fixed factors; and baseline value as covariate, with compound symmetry covariance structure.

Source: Clinical Study Report for Study CL303.[12]

Table 57: Change From Baseline to Week 24 in BPI Worst Pain Score, WOMAC Stiffness Score, and WOMAC Physical Function Score in Study CL303

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Worst pain, by BPI		
Baseline, n	68	66
Mean (SD)	6.81 (1.308)	6.54 (1.433)
Week 24, n	67	65
Mean (SD)	5.82 (1.916)	6.09 (2.013)
LS mean (95% CI) change from baseline	−0.79 (−1.20 to −0.37)	−0.32 (−0.76 to 0.11)
LS mean (95% CI) difference (burosumab minus placebo)	−0.46 (−1.00 to 0.08)	
P value	0.0919	
Significance level for test	0.05	
Significant?	No	
Physical functioning, by WOMAC		

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Baseline, n	68	66
Mean (SD)	50.79 (19.660)	43.89 (19.938)
Week 24, n	66	65
Mean (SD)	43.43 (19.507)	42.65 (22.760)
LS mean (95% CI) change from baseline	−3.11 (−8.12 to 1.89)	1.79 (−3.54 to 7.13)
LS mean (95% CI) difference (burosumab – placebo)	−4.90 (−9.76 to −0.05)	
P value	0.0478	
Significance level for test	0.025	
Significant?	No	
Stiffness, by WOMAC		
Baseline, n	68	66
Mean (SD)	64.71 (20.253)	61.36 (20.770)
Week 24, n	67	65
Mean (SD)	53.73 (20.759)	60.38 (21.827)
LS mean (95% CI) change from baseline	−7.85 (−13.80 to −1.91)	0.46 (−5.70 to 6.61)
LS mean (95% CI) difference (burosumab – placebo)	−8.31 (−14.68 to −1.94)	
P value	0.0106	
Significance level for test	0.0167	
Significant?	Yes	

BPI = Brief Pain Inventory; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Note: The estimates of LS means and P values are from the GEE model, which includes the change from baseline for the end point of interest as the dependent variable; region, visit, treatment, actual randomization stratification (not included for analysis of BPI worst pain) and visit by treatment as fixed factors; and baseline value for the end point of interest as a covariate, with compound symmetry covariance structure.

Source: Clinical Study Report for Study CL303.[12]

Table 58: Change From Baseline to Week 24 in BPI Worst Pain Score by Subgroups of Baseline BPI Worst Pain (≤ 6.0, > 6.0), Baseline WOMAC Physical Function Score (≤ 47.8, > 47.8), Baseline WOMAC Stiffness Score (≤ 62.5, > 62.5), and Presence of Active Fractures or Pseudofractures at Baseline (Yes, No) in Study CL303

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Subgroup of baseline BPI worst pain ≤ 6.0[ab]		
Baseline, n	15	23
Mean (SD)	4.86 (0.895)	5.02 (0.895)
Week 24, n	15	23
LS mean (95% CI) difference (burosumab minus placebo)	−0.48 (−1.41 to 0.44)	
P value	0.3057	
Subgroup of baseline BPI worst pain > 6.0 [ab]		

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Baseline, n	52	42
Mean (SD)	7.36 (0.776)	7.33 (0.881)
Week 24, n	52	42
LS mean (95% CI) difference (burosumab minus placebo)	−0.53 (−1.17 to 0.11)	
P value	0.1028	
Subgroup of baseline WOMAC stiffness score ≤ 62.5[c]		
Baseline, n	39	41
Mean (SD)	6.37 (1.440)	6.28 (1.503)
Week 24, n	39	41
LS mean (95% CI) difference (burosumab minus placebo)	−0.49 (−1.15 to 0.16)	
P value	0.1376	
Subgroup of baseline WOMAC stiffness score > 62.5[c]		
Baseline, n	28	24
Mean (SD)	7.39 (0.830)	6.91 (1.184)
Week 24, n	28	24
LS mean (95% CI) difference (burosumab minus placebo)	−0.44 (−1.39 to 0.51)	
P value	0.3649	
Subgroup of baseline WOMAC physical function score ≤ 47.8[d]		
Baseline, n	30	37
Mean (SD)	6.19 (1.433)	6.13 (1.262)
Week 24, n	30	37
LS mean (95% CI) difference (burosumab minus placebo)	−0.36 (−1.07 to 0.34)	
P value	0.3158	
Subgroup of baseline WOMAC physical function score > 47.8[d]		
Baseline, n	37	28
Mean (SD)	7.29 (0.987)	7.02 (1.475)
Week 24, n	37	28
LS mean (95% CI) difference (burosumab minus placebo)	−0.73 (−1.49 to 0.03)	
P value	0.0615	
Patients with baseline active fractures or active pseudofractures[e]		
Baseline, n	31	37
Mean (SD)	6.59 (1.323)	6.80 (1.232)
Week 24, n	31	37
LS mean (95% CI) difference (burosumab minus placebo)	−0.58 (−1.33 to 0.18)	
P value	NR	
Patients without baseline active fractures or active pseudofractures[e]		
Baseline, n	36	28
Mean (SD)	6.98 (1.302)	6.13 (1.571)
Week 24, n	36	28

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
LS mean (95% CI) difference (burosumab minus placebo)	−0.37 (−1.22 to 0.49)	
P value	NR	
Patients with history of bone fractures[f]		
Baseline, n	29	29
Mean (SD)	6.54 (1.464)	6.94 (1.303)
Week 24, n	29	29
LS mean (95% CI) difference (burosumab minus placebo)	NR	
P value	NR	

BPI = Brief Pain Inventory; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; NR = not reported; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Baseline BPI worst pain is defined as the mean of the BPI worst pain score for 8 days, including the 7 days of diary scores prior to baseline visit and the baseline visit score.

[b] The GEE estimates are from the GEE model, which includes the change from baseline for BPI worst pain as the dependent variable; region, visit, treatment, and visit by treatment as fixed factors; and baseline of BPI worst pain as covariate, with compound symmetry covariance structure for each level of the subgroup variable. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[c] The GEE estimates are from the GEE model, which includes the change from baseline for BPI worst pain as the dependent variable; region, baseline WOMAC stiffness (≤ 62.5 or > 62.5), visit, treatment and visit by treatment, visit by baseline WOMAC stiffness, treatment by baseline WOMAC stiffness, and treatment by baseline WOMAC stiffness by visit as fixed factors; and baseline of BPI worst pain as covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[d] The GEE estimates are from the GEE model, which includes the change from baseline for BPI worst pain as the dependent variable; region, baseline WOMAC physical function (≤ 47.8 or > 47.8), visit, treatment and visit by treatment, visit by baseline WOMAC physical function, treatment by baseline WOMAC physical function, and treatment by baseline WOMAC physical function by visit as fixed factors; and baseline of BPI worst pain as covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[e] The GEE estimates are from the GEE model, which includes the change from baseline for BPI worst pain as the dependent variable, region, baseline active fractures or active pseudofractures (yes or no), visit, treatment and visit by treatment, visit by baseline active fractures or active pseudofractures, treatment by baseline active fractures or active pseudofractures, and treatment by baseline active fractures or active pseudofractures by visit as fixed factors; and baseline of BPI worst pain as covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[f] The GEE estimates are from the GEE model, which includes the change from baseline for BPI worst pain as the dependent variable; region, visit, treatment, and visit by treatment as fixed factors; and baseline of BPI worst pain as covariate, with compound symmetry covariance structure.

Source: Additional information;[70] Clinical Study Report for Study CL303.[12]

Table 59: Change From Baseline to Week 24 in WOMAC Physical Function Score by Subgroups of Baseline BPI Worst Pain (≤ 6.0, > 6.0), Baseline WOMAC Physical Function Score (≤ 47.8, > 47.8), Baseline WOMAC Stiffness Score (≤ 62.5, > 62.5), and Presence of Active Fractures or Pseudofractures at Baseline (Yes, No) in Study CL303

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Subgroup of baseline BPI worst pain ≤ 6.0[ab]		
Baseline, n	15	23
Mean (SD)	33.82 (17.141)	33.25 (18.462)
Week 24, n	15	23
LS mean (95% CI) difference (burosumab minus placebo)	−2.20 (−8.80 to 4.40)	
P value	0.5137	

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Subgroup of baseline BPI worst pain > 6.0 [ab]		
Baseline, n	51	42
Mean (SD)	55.18 (17.264)	49.30 (18.602)
Week 24, n	51	42
LS mean (95% CI) difference (burosumab minus placebo)	−6.05 (−12.22 to 0.11)	
P value	0.0540	
Subgroup of baseline WOMAC stiffness score ≤ 62.5[c]		
Baseline, n	38	41
Mean (SD)	42.32 (18.227)	39.67 (20.884)
Week 24, n	38	41
LS mean (95% CI) difference (burosumab minus placebo)	−1.45 (−7.71 to 4.81)	
P value	0.6505	
Subgroup of baseline WOMAC stiffness score > 62.5[c]		
Baseline, n	28	24
Mean (SD)	61.19 (15.243)	50.37 (16.600)
Week 24, n	28	24
LS mean (95% CI) difference (burosumab minus placebo)	−9.97 (−17.14 to −2.81)	
P value	0.0063	
Subgroup of baseline WOMAC physical function score ≤ 47.8[d]		
Baseline, n	29	37
Mean (SD)	32.45 (11.692)	29.77 (13.578)
Week 24, n	29	37
LS mean (95% CI) difference (burosumab minus placebo)	−0.33 (−6.23 to 5.57)	
P value	0.9128	
Subgroup of baseline WOMAC physical function score > 47.8[d]		
Baseline, n	37	28
Mean (SD)	64.33 (10.476)	61.92 (9.432)
Week 24, n	37	28
LS mean (95% CI) difference (burosumab minus placebo)	−8.78 (−16.35 to −1.20)	
P value	0.0232	
Patients with baseline active fractures or active pseudofractures[e]		
Baseline, n	30	37
Mean (SD)	49.90 (19.367)	45.91 (18.008)
Week 24, n	30	37
LS mean (95% CI) difference (burosumab minus placebo)	−7.73 (−14.80 to −0.67)	
P value	NR	
Patients without baseline active fractures or active pseudofractures[e]		
Baseline, n	36	28
Mean (SD)	50.68 (19.577)	40.60 (22.271)
Week 24, n	36	28

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
LS mean (95% CI) difference (burosumab minus placebo)	−1.88 (−8.99 to 5.23)	
P value	NR	
Patients with history of bone fractures[f]		
Baseline, n	29	29
Mean (SD)	49.09 (21.167)	48.83 (16.911)
Week 24, n	29	29
LS mean (95% CI) difference (burosumab minus placebo)	NR	
P value	NR	

BPI = Brief Pain Inventory; CI = confidence interval; GEE = generalized estimating equation; LS = least squares; NR = not reported; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Baseline BPI worst pain is defined as the mean of the BPI worst pain score for 8 days, including the 7 days of diary scores prior to baseline visit and the baseline visit score.

[b] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC physical function as the dependent variable; region, visit, treatment, baseline BPI worst pain (> 6.0 or ≤ 6.0) and visit by treatment, visit by baseline BPI worst pain (> 6.0 or ≤ 6.0), treatment by baseline BPI worst pain (> 6.0 or ≤ 6.0), and treatment by baseline BPI worst pain (> 6.0 or ≤ 6.0) by visit as fixed factors; and baseline of WOMAC physical function as covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[c] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC physical function as the dependent variable; region, visit, treatment, actual randomization stratification, baseline WOMAC stiffness (≤ 62.5 or > 62.5) and visit by treatment, visit by baseline WOMAC stiffness, treatment by baseline WOMAC stiffness, and treatment by baseline WOMAC stiffness by visit as fixed factors; and baseline of WOMAC physical function as covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[d] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC physical function as the dependent variable; region, visit, treatment, actual randomization stratification, and visit by treatment as fixed factors; and baseline of WOMAC physical function as covariate, with compound symmetry covariance structure for each level of the subgroup variable. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[e] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC physical function as the dependent variable; region, visit, treatment, actual randomization stratification, baseline active fractures or active pseudofractures (yes or no) and visit by treatment, visit by baseline active fractures or active pseudofractures, treatment by baseline active fractures or active pseudofractures, and treatment by baseline active fractures or active pseudofractures by visit as fixed factors; and baseline of WOMAC physical function as covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[f] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC physical function as the dependent variable; region, visit, treatment, actual randomization stratification, and visit by treatment as fixed factors; and baseline of WOMAC physical function as covariate, with compound symmetry covariance structure.

Source: Additional information;[70] Clinical Study Report for Study CL303.[12]

Table 60: Change From Baseline to Week 24 in WOMAC Stiffness Score by Subgroups of Baseline BPI Worst Pain (≤ 6.0, > 6.0), Baseline WOMAC Physical Function Score (≤ 47.8, > 47.8), Baseline WOMAC Stiffness Score (≤ 62.5, > 62.5), and Presence of Active Fractures or Pseudofractures at Baseline (Yes, No) in Study CL303

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Subgroup of baseline BPI worst pain ≤ 6.0[ab]		
Baseline, n	15	23
Mean (SD)	50.83 (15.285)	50.00 (20.643)
Week 24, n	15	23
LS mean (95% CI) difference (burosumab minus placebo)	−9.24 (−18.45 to –0.03)	
P value	0.0492	
Subgroup of baseline BPI worst pain > 6.0 [ab]		
Baseline, n	52	42
Mean (SD)	68.27 (19.874)	67.26 (18.510)
Week 24, n	52	42
LS mean (95% CI) difference (burosumab minus placebo)	−8.63 (−16.82 to −0.44)	
P value	0.0389	
Subgroup of baseline WOMAC stiffness score ≤ 62.5[c]		
Baseline, n	39	41
Mean (SD)	50.96 (13.868)	49.39 (16.045)
Week 24, n	39	41
LS mean (95% CI) difference (burosumab minus placebo)	−6.52 (−14.77 to 1.74)	
P value	0.1218	
Subgroup of baseline WOMAC stiffness score > 62.5[c]		
Baseline, n	28	24
Mean (SD)	83.04 (10.327)	81.25 (9.752)
Week 24, n	28	24
LS mean (95% CI) difference (burosumab minus placebo)	−10.98 (−20.96 to −1.01)	
P value	0.0309	
Subgroup of baseline WOMAC physical function score ≤ 47.8[d]		
Baseline, n	30	37
Mean (SD)	53.75 (18.613)	54.39 (20.669)
Week 24, n	30	37
LS mean (95% CI) difference (burosumab minus placebo)	−8.05 (−15.89 to −0.21)	
P value	0.0441	
Subgroup of baseline WOMAC physical function score > 47.8[d]		
Baseline, n	37	28
Mean (SD)	72.97 (17.309)	70.09 (17.788)
Week 24, n	37	28
LS mean (95% CI) difference (burosumab minus placebo)	−9.65 (−18.98 to −0.32)	

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
P value	0.0426	
Patients with baseline active fractures or active pseudofractures[e]		
Baseline, n	31	37
Mean (SD)	65.32 (22.983)	66.22 (16.368)
Week 24, n	31	37
LS mean (95% CI) difference (burosumab minus placebo)	−10.82 (−20.13 to −1.51)	
P value	NR	
Patients without baseline active fractures or active pseudofractures[e]		
Baseline, n	36	28
Mean (SD)	63.54 (17.772)	54.46 (24.347)
Week 24, n	36	28
LS mean (95% CI) difference (burosumab minus placebo)	−5.02 (−14.08 to 4.04)	
P value	NR	
Patients with history of bone fractures[f]		
Baseline, n	29	29
Mean (SD)	67.24 (18.424)	68.53 (18.182)
Week 24, n	29	29
LS mean (95% CI) difference (burosumab minus placebo)	NR	
P value	NR	

CI = confidence interval; BPI = Brief Pain Inventory; GEE = generalized estimating equation; LS = least squares; SD = standard deviation; NR = not reported; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Baseline BPI worst pain is defined as the mean of the BPI worst pain score for 8 days, including the 7 days of diary scores prior to baseline visit and the baseline visit score.

[b] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC stiffness as the dependent variable; region, visit, treatment, baseline BPI worst pain (> 6.0 or ≤ 6.0) and visit by treatment, visit by baseline BPI worst pain (> 6.0 or ≤ 6.0), treatment by baseline BPI worst pain (> 6.0 or ≤ 6.0), and treatment by baseline BPI worst pain (> 6.0 or ≤ 6.0) by visit as fixed factors; and baseline of WOMAC stiffness as covariate, with compound symmetry covariance structure.

[c] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC stiffness as the dependent variable; region, visit, treatment, actual randomization stratification, and visit by treatment as fixed factors; and baseline of WOMAC stiffness as covariate, with compound symmetry covariance structure for each level of the subgroup variable. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[d] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC stiffness as the dependent variable; region, baseline WOMAC physical function (≤ 47.8 or > 47.8), visit, treatment and visit by treatment, visit by baseline WOMAC physical function, treatment by baseline WOMAC physical function, and treatment by baseline WOMAC physical function by visit as fixed factors; and baseline of WOMAC stiffness as covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[e] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC stiffness as the dependent variable; region, visit, treatment, actual randomization stratification, baseline active fractures or active pseudofractures (yes or no) and visit by treatment, visit by baseline active fractures or active pseudofractures, treatment by baseline active fractures or active pseudofractures, and treatment by baseline active fractures or active pseudofractures by visit as fixed factors; and baseline of WOMAC stiffness as covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit of that specified category.

[f] The GEE estimates are from the GEE model, which includes the change from baseline for WOMAC stiffness as the dependent variable; region, visit, treatment, actual randomization stratification, and visit by treatment as fixed factors; and baseline of WOMAC stiffness as covariate, with compound symmetry covariance structure.

Source: Additional information;[70] Clinical Study Report for Study CL303.[12]

Table 61: Change From Baseline to Week 24 in BPI Pain Severity, BPI Pain Interference, BFI Worst Fatigue, and BFI Global Fatigue in Study CL303

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
BPI pain severity		
Baseline, n	68	66
Mean (SD)	5.18 (1.53)	4.92 (1.55)
Range	1.8 to 8.3	1.2 to 7.9
Week 24, n	67	65
LS mean (95% CI) change from baseline	−0.59 (−0.91 to −0.27)	−0.16 (−0.55 to 0.22)
LS mean (95% CI) difference (burosumab minus placebo)	−0.43 (−0.93 to 0.07)	
P value	0.0926	
BPI pain interference	67	65
Baseline, n	68	66
Mean (SD)	5.23 (2.24)	4.76 (2.17)
Range	0.1 to 10.0	0.0 to 10.0
Week 24	67	65
LS mean (95% CI) change from baseline	−0.40 (−0.85 to 0.04)	−0.27 (−0.78 to 0.23)
LS mean (95% CI) difference (burosumab minus placebo)	−0.13 (−0.70 to 0.44)	
P value	0.6511	
BFI worst fatigue		
Baseline, n	68	66
Mean (SD)	6.94 (1.66)	6.74 (1.53)
Range	2.8 to 9.8	3.6 to 9.9
Week 24, n	67	65
LS mean (95% CI) change from baseline[a]	−0.67 (−1.21 to −0.12)	−0.47 (−1.03 to 0.09)
LS mean (95% CI) difference (burosumab minus placebo)	−0.20 (−0.80 to 0.40)	
P value	0.5150	
BFI global fatigue		
Baseline, n	68	66
Mean (SD)	5.37 (2.04)	4.86 (1.93)
Range	1.2 to 8.8	0.7 to 9.0
Week 24, n	67	65
LS mean (95% CI) change from baseline[a]	0.04 (−0.48 to 0.57)	−0.07 (−0.66 to 0.53)
LS mean (95% CI) difference (burosumab minus placebo)	0.11 (−0.46 to 0.67)	
P value	0.7129	

CI = confidence interval; BFI = Brief Fatigue Inventory; BPI = Brief Pain Inventory; GEE = generalized estimating equation; LS = least squares; SD = standard deviation.

[a] The GEE estimates are from the GEE model, which includes the change from baseline for each BPI end point as the dependent variable; region, visit, treatment, and visit by treatment as fixed factors; and baseline of each BPI end point as a covariate, with compound symmetry covariance structure. The baseline summary at each post-baseline visit is based on baseline of the patients who had non-missing results at the given visit.

Source: Clinical Study Report for Study CL303.[12]

Table 62: FPS – Revised by Treatment Group (Baseline Age ≥ 5 Years) in Study CL301

	Burosumab every two weeks (N = 15)	Phosphate and active vitamin D (N = 20)
Baseline – n	15	20
Mean (SD)	0.4 (1.12)	0.7 (1.17)
Week 40 – n	15	20
Mean (SD)	0.5 (1.19)	0.6 (1.60)
Change from baseline to week 40, LS mean (95% CI)[a]	0.04 (−0.57 to 0.65)	0.04 (−0.60 to 0.69)
Difference (burosumab minus active control) (95% CI)[a]	−0.00 (−0.80 to 0.79)	
P value[a]	0.9905	
Week 64 – n	15	19
Mean (SD)	0.5 (0.92)	0.5 (1.12)
Change from baseline to week 64, LS mean (95% CI)[a]	0.04 (−0.49 to 0.57)	−0.01 (−0.47 to 0.45)
Difference (burosumab minus active control) (95% CI)[a]	0.05 (−0.58 to 0.68)	
P value[a]	0.8786	

CI = confidence interval; FPS = Faces Pain Scale; FPS-R = Faces Pain Scale – Revised; GEE = generalized estimating equation; LS = least squares; RSS = Rickets Severity Score; SE = standard error.

[a] The GEE model includes change from baseline for FPS-R as the dependent variable; treatment group, visit, interaction between treatment group by visit, and baseline RSS stratification as factors; and baseline FPS-R as a covariate, with exchangeable covariance structure. The LS mean, SE, 95% CI, and 2-sided P value are from the GEE model.

Source: Clinical Study Report for Study CL301.[13]

Table 63: 6MWT and Percentage of Predicted 6MWT by Treatment Group (Baseline Age ≥ 5 Years) in Study CL301

	Burosumab every two weeks (N = 15)	Phosphate and active vitamin D (N = 20)
6MWT[a] (m walked)		
Baseline – n	13	20
Mean (SD)	385 (86)	451 (106)
Week 40 – n	13	20
Mean (SD)	435 (86)	457 (96)
Change from baseline to week 40, LS mean (95% CI)[a]	47 (16 to 78)	4 (−24 to 31)
Difference (burosumab minus active control) (95% CI)[a]	43 (−0.3 to 87)	
P value[a]	0.0514	
Week 64 – n	13	20
Mean (SD)	466 (82)	481 (113)
Change from baseline to week 64, LS mean (95% CI)[a]	75 (50 to 99)	29 (−4 to 62)
Difference (burosumab minus active control) (95% CI)[a]	+46 (2 to 89)	
P value[a]	0.0399	
Percentage of predicted 6MWT[a]		
Baseline – n	13	20
Mean (SD)	65.1 (12.1)	76.2 (14.8)
Week 40 – n	13	20

	Burosumab every two weeks (N = 15)	Phosphate and active vitamin D (N = 20)
Mean (SD)	71.6 (12.8)	75.3 (14.2)
Change from baseline to week 40, LS mean (95% CI)[a]	5.6 (0.43 to 10.75)	−1.1 (−5.49 to 3.22)
Difference (burosumab minus active control) (95% CI)[a]	6.7 (−0.4 to 13.8)	
P value[a]	0.0633	
Week 64 – n	13	20
Mean (SD)	75.5 (11.6)	78.1 (17.5)
Change from baseline to week 64, LS mean (95% CI)[a]	9.2 (5.1 to 13.2)	1.9 (−3.6 to 7.4)
Difference (burosumab minus active control) (95% CI)[a]	7.3 (0.01 to 14.5)	
P value[a]	0.0496	

6MWT = 6-minute walk test; CI = confidence interval; LS = least squares; GEE = generalized estimating equation; RSS = Rickets Severity Score; SD = standard deviation; SE = standard error.

Note: The analyses shown in the table exclude 2 patients in the burosumab group who did not complete the 6MWT.

[a] LS mean, SE, CI, and 2-sided P value per GEE model, which included change from baseline for 6MWT as the dependent variable; treatment group, visit, interaction between treatment group by visit, and baseline RSS stratification as factors; and baseline 6MWT as a covariate, with exchangeable covariance structure

Source: Clinical Study Report for Study CL301.[13]

Table 64: 6MWT Distance (in Metres and Predicted Percentage of Normal) Change From Baseline to Week 64 by RSS Subgroup and Baseline Predicted 6MWT Subgroup (ITT Analysis Set) in Study CL201

	Study CL201	
	Burosumab every two weeks (N = 26)	
	6MWT distance (distance walked [m])	6MWT distance (predicted % of normal)
All patients		
n	26	26
Baseline, mean (SD)	479.92 (84.802)	79.32 (13.257)
Week 64, mean (SD)	533.85 (58.699)	85.00 (10.326)
Change to week 64, LS mean (95% CI)[a]	+52.67 (35.39 to 69.95)	+5.29 (2.22 to 8.36)
P value	< 0.0001	0.0007
Baseline predicted 6MWT < 80% subgroup		
n	14	14
Baseline, mean (SD)	424.64 (63.431)	70.09 (9.148)
Week 64, mean (SD)	509.86 (54.308)	81.49 (10.387)
Change to week 64, LS mean (95% CI)[a]	+95.54 (72.02 to 119.06)	+12.32 (8.16 to 16.49)
P value	< 0.0001	< 0.0001
Baseline predicted 6MWT ≥ 80% subgroup		
n	12	12
Baseline, mean (SD)	544.42 (56.232)	90.09 (8.098)
Week 64, mean (SD)	561.83 (52.520)	89.10 (8.991)
Change to week 64, LS mean (95% CI)[a]	+16.88 (−7.67 to 41.44)	−1.04 (−4.92 to 2.83)
P value	0.1777	0.5977

	Study CL201	
	Burosumab every two weeks (N = 26)	
	6MWT distance (distance walked [m])	6MWT distance (predicted % of normal)
Baseline RSS total score ≥ 1.5		
n	17	17
Baseline, mean (SD)	446.82 (78.621)	73.27 (11.021)
Week 64, mean (SD)	510.24 (50.390)	81.10 (9.455)
Change to week 64, LS mean (95% CI)[a]	55.82 (30.61 to 81.02)	6.39 (1.74 to 11.03)
P value	< 0.0001	0.0070
Baseline RSS total score < 1.5		
n	9	9
Baseline, mean (SD)	542.44 (58.179)	90.74 (9.042)
Week 64, mean (SD)	578.44 (47.611)	92.38 (7.801)
Change to week 64, LS mean (95% CI)[a]	50.27 (30.12 to 70.42)	3.96 (0.71 to 7.20)
P value	< 0.0001	0.0169

6MWT = 6-minute walk test; CI = confidence interval; GEE = generalized estimating equation; ITT = intention to treat; LS = least squares; RSS = Rickets Severity Score; SD = standard deviation; SE = standard error.

[a] The GEE model included change in 6MWT score as the dependent variable; visit, regimen, and visit by regimen as factors; and 6MWT at baseline as a covariate, with exchangeable covariance structure. The LS mean, SE, and 2-sided P value are from the GEE model.

Source: Clinical Study Report for Study CL201.[10]

Table 65: Change From Baseline in 6-Minute Walk Test (Total Distance Walked and Percentage of Predicted Distance) in Study CL303

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
6-minute walk test (total distance walked m)		
Baseline, n	65	64
Mean (SD)	359.51 (109.629)	367.28 (104.22)
Range	55 to 643	160 to 615
At week 24, n	65	64
Mean (SD)	381.45 (108.46)	369.44 (103.39)
LS mean (95% CI) change from baseline[a]	17.12 (2.50 to 31.75)	−2.81 (−17.64 to 12.02)
LS mean (95% CI) difference (burosumab minus placebo)[a]	19.93 (4.38 to 35.49)	
P value	0.0120	
6-minute walk test percentage of predicted distance		
Baseline, n	65	64
Mean (SD)	51.87 (15.81)	52.16 (15.00)
Range	7.6 to 92.4	23.1 to 88.4
At week 24, n	65	64
Mean (SD)	55.19 (15.857)	52.42 (14.33)
LS mean (95% CI) change from baseline[a]	2.44 (0.32 to 4.55)	−0.76 (−2.80 to 1.28)

	Study CL303	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)
LS mean (95% CI) difference (burosumab minus placebo)[a]	3.19 (0.98 to 5.41)	
P value	0.0047	

6MWT = 6-minute walk test; CI = confidence interval; GEE = generalized estimating equation; SD = standard deviation.

[a] The GEE estimates are from the GEE model, which includes the change from baseline for each 6MWT end point as the dependent variable; region, visit, treatment, actual randomization stratification, and visit by treatment as fixed factors; and baseline of each 6MWT end point as a covariate, with compound symmetry covariance structure.

Source: Clinical Study Report for Study CL303.[12]

Table 66: PROMIS Domains by Treatment Group (Baseline Age ≥ 5 Years) in Study CL301

	Burosumab every two weeks (N = 15)	Phosphate and active vitamin D (N = 20)
Pain interference domain score (decrease indicates less pain)		
Baseline – n	15	20
Mean (SD)	53.1 (10.95)	49.9 (12.05)
Week 40 – n	15	20
Mean (SD)	47.6 (9.84)	50.4 (9.51)
Difference (burosumab minus active control) (95% CI)[a]	−5.02 (−9.29 to −0.75)	
P value[a]	0.0212	
Week 64 – n	15	20
Mean (SD)	49.3 (8.07)	49.4 (9.52)
Difference (burosumab minus active control) (95% CI)[a]	−2.26 (−6.61 to 2.09)	
P value[a]	0.3091	
Physical function mobility domain score (increase indicates greater mobility)		
Baseline – n	15	20
Mean (SD)	45.2 (9.05)	45.5 (9.86)
Week 40 – n	15	20
Mean (SD)	47.9 (8.32)	45.5 (9.71)
Difference (burosumab minus active control) (95% CI)[a]	2.68 (−0.52 to +5.89)	
P value[a]	0.1009	
Week 64 – n	15	20
Mean (SD)	47.9 (9.24)	46.3 (9.63)
Difference (burosumab minus active control) (95% CI)[a]	1.90 (−1.80 to 5.59)	
P value[a]	0.3145	
Fatigue domain score (decrease indicates less fatigue)		
Baseline – n	15	20
Mean (SD)	48.8 (9.60)	47.0 (13.70)
Week 40 – n	15	20
Mean (SD)	44.7 (10.49)	46.6 (10.73)
Difference (burosumab minus active control) (95% CI)[a]	−3.25 (−7.86 to +1.37)	
P value[a]	0.1676	

	Burosumab every two weeks (N = 15)	Phosphate and active vitamin D (N = 20)
Week 64 – n	15	20
Mean (SD)	45.2 (10.69)	45.0 (11.17)
Difference (burosumab minus active control) (95% CI)[a]	−1.08 (−6.21 to 4.06)	
P value[a]	0.6810	

CI = confidence interval; GEE = generalized estimating equation; LS = least squares; PROMIS = Patient-Reported Outcomes Measurement Information System; RSS = Rickets Severity Score; LS = least squares; SD = standard deviation; SE = standard error.

[a] LS mean, SE, CI, and 2-sided P value per GEE model, which included change from baseline for PROMIS domain score as the dependent variable; treatment group, visit, interaction between treatment group by visit, and baseline RSS stratification as factors; and baseline domain score as covariate, with exchangeable covariance structure.

Source: Clinical Study Report for CL301.[13]

Table 67: POSNA-PODCI Sports and Physical Functioning Scale and Pain and Comfort Scale Change From Baseline to Week 64 by RSS Subgroup and Baseline Global Functioning Scale Subgroup (ITT Analysis Set) in Study CL201

	Study CL201	
	Burosumab every two weeks (N = 26)	
	Sports and physical functioning scale (normative score)	Pain and comfort scale (normative score)
All patients		
n	26	26
Baseline, mean (SD)	34.6 (15.70)	35.2 (15.26)
Week 64, mean (SD)	41.7 (15.67)	41.0 (17.04)
Change to week 64, LS mean (95% CI)[a]	+7.74 (2.58 to 12.91)	+5.60 (−0.09 to 11.30)
P value	0.0033	0.0536
Baseline RSS total score ≥ 1.5		
n	17	17
Baseline, mean (SD)	30.3 (14.51)	29.4 (13.67)
Week 64, mean (SD)	38.5 (17.67)	40.5 (16.41)
Change to week 64, LS mean (95% CI)[a]	+8.62 (0.98 to 16.25)	+10.57 (3.71 to 17.44)
P value	0.0270	0.0025
Baseline RSS total score < 1.5		
n	9	9
Baseline, mean (SD)	42.7 (15.38)	46.3 (11.92)
Week 64, mean (SD)	47.8 (8.87)	41.9 (19.15)
Change to week 64, LS mean (95% CI)[a]	+6.12 (3.56 to 8.69)	−3.87 (−12.81 to 5.07)
P value	< 0.0001	0.3963
Baseline global functioning scale normative score < 40 subgroup		
n	14	14
Baseline, mean (SD)	24.6 (13.03)	24.9 (11.60)
Week 64, mean (SD)	36.0 (18.46)	38.3 (21.07)

	Study CL201	
	Burosumab every two weeks (N = 26)	
	Sports and physical functioning scale (normative score)	Pain and comfort scale (normative score)
Change to week 64, LS mean (95% CI)[a]	+13.55 (4.32 to 22.77)	+13.91 (3.88 to 23.95)
P value	0.0040	0.0066
Baseline global functioning scale normative score ≥ 40 subgroup		
n	12	12
Baseline, mean (SD)	46.3 (9.14)	47.3 (8.57)
Week 64, mean (SD)	48.3 (8.11)	44.2 (10.70)
Change to week 64, LS mean (95% CI)[a]	+1.63 (−1.53 to 4.79)	−3.83 (−8.23 to 0.57)
P value	0.3123	0.0882

CI = confidence interval; GEE = generalized estimating equation; ITT = intention to treat; LS = least squares; PODCI = Pediatric Outcomes Data Collection Instrument; POSNA = Pediatric Orthopaedic Society of North America; RSS = Rickets Severity Score; SD = standard deviation; SE = standard error.

[a] The GEE model included change in POSNA-PODCI scale score as the dependent variable; visit, regimen, and visit by regimen as factors; and POSNA-PODCI scale score at baseline as covariate, with exchangeable covariance structure. The LS mean, SE, and 2-sided P value are from the GEE model.

Source: Clinical Study Report for Study CL201.[10]

Table 68: Bruininks-Oseretsky Test of Motor Proficiency – Second Edition (ITT Analysis Set) in Study CL201

	Study CL201
	Burosumab every two weeks (N = 26)
Running speed and agility scaled score	
n	25
Baseline, mean (SD)	11.1 (4.85)
Week 64, mean (SD)	14.2 (4.09)
Change to week 64, mean (SD)	3.0 (3.66)
P value	NR
Strength scaled score	
n	25
Baseline, mean (SD)	14.2 (5.00)
Week 64, mean (SD)	15.1 (5.26)
Change to week 64, mean (SD)	0.9 (1.94)
P value	NR
Strength and agility standard score	
n	25
Baseline, mean (SD)	43.9 (9.39)
Week 64, mean (SD)	48.3 (10.95)
Change to week 64, mean (SD)	4.4 (5.87)
P value	NR
Strength and agility percentile rank	
n	25

	Study CL201
	Burosumab every two weeks (N = 26)
Baseline, mean (SD)	33.4 (25.98)
Week 64, mean (SD)	47.6 (27.72)
Change to week 64, mean (SD)	14.2 (11.98)
P value	NR

ITT = intention to treat; NR = not reported; SD = standard deviation.

Source: Clinical Study Report for Study CL201.[10]

Table 69: SF-10 (Baseline Age ≥ 5 Years) in Study CL301

	Burosumab every two weeks (N = 15)	Phosphate and active vitamin D (N = 20)
Physical summary score		
Baseline – n	15	20
Mean (SD)	40.033 (10.0690)	40.738 (15.2984)
Week 40 – n	15	20
Mean (SD)	46.161 (9.9043)	42.273 (12.5101)
Change from baseline, mean (SD)	6.127 (7.9280)	1.535 (12.2146)
Week 64 – n	15	20
Mean (SD)	46.115 (9.8443)	41.070 (15.0930)
Change from baseline, mean (SD)	6.082 (8.4706)	0.332 (10.8116)
Psychosocial summary score		
Baseline – n	15	20
Mean (SD)	50.755 (9.6521)	52.789 (9.4015)
Week 40 – n	15	20
Mean (SD)	52.656 (9.2245)	51.853 (9.3300)
Change from baseline, mean (SD)	1.901 (6.7320)	–0.936 (6.7943)
Week 64 – n	15	20
Mean (SD)	52.062 (9.1366)	53.948 (8.4566)
Change from baseline, mean (SD)	1.307 (8.1797)	1.159 (6.2365)

SD = standard deviation; SF-10 = Short Form (10) Health Survey for Children.

Source: Clinical Study Report for Study CL301.[13]

Table 70: SF-10 (ITT Analysis Set) in Study CL201

	Burosumab every two weeks (N = 26)
Physical summary score	
Baseline – n	26
Mean (SD)	41.572 (12.1365)
Week 40 – n	25
Mean (SD)	49.237 (8.1466)
Change from baseline, mean (SD)	6.784 (13.2142)

	Burosumab every two weeks (N = 26)
Week 64 – n	26
Mean (SD)	47.406 (10.4325)
Change from baseline, mean (SD)	5.834 (12.8870)
Psychosocial summary score	
Baseline – n	26
Mean (SD)	53.369 (9.5187)
Week 40 – n	25
Mean (SD)	55.758 (8.4852)
Change from baseline, mean (SD)	1.283 (7.9063)
Week 64 – n	26
Mean (SD)	52.853 (8.4696)
Change from baseline, mean (SD)	−0.516 (7.8038)

ITT = intention to treat; SD = standard deviation; SF-10 = Short Form (10) Health Survey for Children.

Source: Clinical Study Report for Study CL201.[10]

Table 71: Summary of Dental Assessments (Safety Analysis Set) in Study CL301

	Burosumab every two weeks (N = 29)	Phosphate and active vitamin D (N = 32)
Post-baseline to week 64		
Any dental condition	12 (41.4)	5 (15.6)
Dental abscess	10 (34.5)	2 (6.3)
Tooth extraction (due to abscess or decay)	5 (17.2)	3 (9.4)
Root canal	3 (10.3)	0 (0.0)
Dental cavities (caries)	6 (20.7)	1 (3.1)
Gingivitis	0 (0.0)	0 (0.0)

Source: Clinical Study Report for Study CL301.[13]

Table 72: Number of Active Fractures and Pseudofractures Healed Over Time and Number of Patients With Active Fractures and Pseudofractures Healed Over Time in Study CL303

	Study CL303			
	Active fractures		Active pseudofractures	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Number of active fracture and pseudofractures				
Baseline	14	13	51	78
Week 12– n (% based on number of cases at baseline)				
Healed	2 (14.3)	0	11 (21.6)	7 (9.0)
Partially healed	8 (57.1)	2 (15.4)	18 (35.3)	22 (28.2)
Unchanged	3 (21.4)	11 (84.6)	13 (25.5)	26 (33.3)
Worse	0	0	0	10 (12.8)

	Study CL303			
	Active fractures		Active pseudofractures	
	Burosumab every four weeks (N = 68)	Placebo (N = 66)	Burosumab every four weeks (N = 68)	Placebo (N = 66)
Missing	1 (7.1)	0	9 (17.6)	13 (16.7)
New finding	0	2	3	6
Week 24 – n (% based on number of cases at baseline)				
Healed	7 (50.0)	0	21 (41.2)	7 (9.0)
Partially healed	3 (21.4)	6 (46.2)	13 (25.5)	19 (24.4)
Unchanged	3 (21.4)	2 (15.4)	6 (11.8)	39 (50.0)
Worse	0	3 (23.1)	2 (3.9)	8 (10.3)
Missing	1 (7.1)	2 (15.4)	9 (17.6)	5 (6.4)
New finding	1	0	2	0
Number of patients with active fractures and pseudofractures				
Baseline	8	8	29	34
Week 12 – n (% based on number of cases at baseline)				
Healed	2 (25.0)	0	10 (34.5)	5 (14.7)
Partially healed	5 (62.5)	2 (25.0)	15 (51.7)	16 (47.1)
Unchanged	2 (25.0)	6 (75.0)	11 (37.9)	18 (52.9)
Worse	0	0	0	8 (23.5)
Missing	1 (12.5)	0	4 (13.8)	5 (14.7)
New finding[a]	0	2 (3.0)	3 (4.4)	5 (7.6)
Week 24 – n (% based on number of cases at baseline)				
Healed	4 (50.0)	0	15 (51.7)	5 (14.7)
Partially healed	3 (37.5)	4 (50.0)	10 (34.5)	16 (47.1)
Unchanged	2 (25.0)	2 (25.0)	5 (17.2)	22 (64.7)
Worse	0	1 (12.5)	2 (6.9)	7 (20.6)
Missing	1 (12.5)	1 (12.5)	4 (13.8)	1 (2.9)
New finding[a]	1 (1.5)	0	2 (2.9)	0

[a] Percentage for a new finding is based on N.

Source: Clinical Study Report for Study CL303.[12]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- BPI
- BFI
- RSS
- RGI-C
- WOMAC
- 6MWT
- POSNA-PODCI
- OV/BV
- SF-10
- BOT-2
- PROMIS scores for pediatric pain interference, fatigue, and physical function mobility scales
- FPS-R.

Table 73: Outcome Measures Included in Each Study

Outcome measure	Study CL201	Study CL205	Study CL301	Study CL303	Study CL304
BPI				Secondary	Exploratory
BFI				Secondary	Exploratory
RSS	Primary		Secondary		
RGI-C	Secondary	Secondary	Primary		
WOMAC				Secondary	
6MWT	Secondary		Secondary	Exploratory	
POSNA-PODCI	Secondary				
OV/BV					Primary
SF-10	Exploratory		Exploratory		
BOT-2	Exploratory				
PROMIS			Secondary		
FPS-R			Secondary		

6MWT = 6-minute walk test; BFI = Brief Fatigue Inventory; BOT-2 = The Bruininks-Oseretsky Test of Motor Proficiency – Second Edition; BPI = Brief Pain Inventory; FPS-R = Faces Pain Scale-Revised; OV/BV = osteoid volume/bone volume; PODCI = Pediatric Outcomes Data Collection Instrument; POSNA = Pediatric Orthopaedic Society of North America; PROMIS = Patient-Reported Outcomes Measurement Information System; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SF-10 = Short Form (10) Health Survey for Children; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Findings

Table 74: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MCID
BPI	Self-reported, 11-item instrument for assessing pain intensity and pain interference	Demonstrated to be reliable (e.g., internal consistency and test-retest reliability) and valid (e.g., construct, convergent, and discriminative validity).	2-point change for worst pain item in breast cancer patients
BFI	Self-reported, 9-item instrument for assessing fatigue	Construct validity, concurrent validity, and discriminant validity were demonstrated. Reliability was excellent.	Not specified
RSS	A radiographic scoring method to assess the severity of rickets in the wrists and knees	Excellent inter- and intra-rater reliability. Significantly correlated to clinical features of XLH.	Not specified
RGI-C	A radiographic scoring method to assess the severity of rickets and bowing	Good to moderate inter- and intra-rater reliability. Significantly correlated to RSS and other clinical features of hypophosphatasia.	Not specified
WOMAC	A self-administered, validated, disease-specific questionnaire for evaluation of osteoarthritis	Acceptable face and content validity.	Not specified
6MWT	A supervised test to measure the distance a patient can walk over a 6 minutes period	Reliability and validity have been established.	31 m for children and adults, 43 m for adolescents (hypophosphatasia population)
POSNA-PODCI	Self-reported generic questionnaire to measure children's HRQoL	Convergent validity has been demonstrated; adequate test-retest reliability.	Not specified
OV/BV	Amount of unmineralized osteoid relative to the total amount of mineralized and unmineralized bone	Not identified.	Not specified
SF-10	A parent-completed questionnaire intended to assess the health status of children aged 5 years to 18 years of age	Internal consistency and test-retest reliabilities are very satisfactory in a range of clinical samples; construct validity and discriminating ability are satisfactory in a variety of clinical samples.	Not specified
BOT-2	A standardized, norm-referenced test of fine and gross motor skills in individuals 4 years to 21 years of age	Test-retest reliability was excellent.	Not specified
PROMIS	Self-reported measure to assess patient well-being	Reliability and validity were examined. Inconsistent results were reported.	Not specified

Outcome measure	Type	Conclusions about measurement properties	MCID
FPS-R	Self-reported instrument of pain intensity in children	Validity (convergent construct validity), test-retest reliability, and responsiveness were demonstrated in children with procedural pain or those taking medication for pain management.	Not specified

6MWT = 6-minute walk test; BFI = Brief Fatigue Inventory; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency – Second Edition; BPI = Brief Pain Inventory; FPS-R = Faces Pain Scale – Revised; HRQoL = health-related quality of life; MCID = minimal clinically important difference; PODCI = Pediatric Outcomes Data Collection Instrument; POSNA = Pediatric Orthopaedic Society of North America; PROMIS = Patient-Reported Outcomes Measurement Information System; OV/BV = osteoid volume/bone volume; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; SF-10 = Short Form (10) Health Survey for Children; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; XLH = X-linked hypophosphatemia.

Brief Pain Inventory

The BPI is a questionnaire designed to provide information about pain intensity (the sensory dimension, four items) and the degree to which pain interferes with functioning in daily living (the reactive dimension, seven items). It is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials as a core outcome measure of pain.[71] Four items assess a patient's pain intensity — at its worst in the last 24 hours, at its least in the last 24 hours, average pain, and pain right now — using a 0 to 10 numeric rating scale, with 0 representing "no pain" and 10 representing "pain as bad as you can imagine." For the seven items assessing pain interference with functioning, patients are asked to rate how their pain interferes with seven life domains, including general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life, on a similar numeric rating scale.

The anchor points in each item of the interference scale are 0 (no interference) and 10 (complete interference). The scores for the two BPI subscales (pain intensity and pain interference) range from 0 to 10 and are calculated using the mean of their corresponding items' scores. The total BPI score is the mean of the two subscale scores. A high score represents a high pain intensity or pain interference. The BPI also contains supplemental items that allow a patient to indicate treatments or medications they are receiving to treat their pain, the percentage of relief obtained in the past 24 hours from the treatments or medications, and the anatomical location of their pain on a body diagram.[41,42] Although originally developed for evaluation of breast, prostate, colon, rectum, or gynecologic cancer pain, it has also been shown to be a reliable (e.g., in terms of internal consistency and test-retest reliability) and valid (e.g., in terms of construct, convergent, and discriminative validity) instrument for the evaluation of non-malignant chronic pain (e.g., low back pain, osteoarthritis, rheumatoid arthritis, or multiple sclerosis) across various languages. It is also commonly used for non-malignant pain.[41,42]

An overall MCID for the BPI has not been identified in the literature, although a two-point change was suggested by Mathias et al. as a reasonable estimate for the MCID of the BPI worst pain item in breast cancer patients with metastases.[43] An MCID for the BPI in patients with XLH was not identified in the literature.

Brief Fatigue Inventory

The BFI is a self-reported questionnaire to assess the severity of fatigue and the impact of fatigue on daily functioning. Two dimensions are measured in this nine-item instrument: fatigue (three items) and the interference of fatigue on daily life (six items pertaining to general activity, mood, walking ability, normal work, relations with others, and enjoyment of life). The items are measured on a 0 to 10 numeric rating scale. For the dimension of severity of fatigue, 0 represents “no fatigue” and 10 represents “fatigue as bad as you can imagine.” For the dimension of interference from fatigue, 0 represents “does not interfere” and 10 represents “completely interferes.” A score of 7 to 10 is considered severe fatigue.[44] A global fatigue score can be obtained by averaging all the items on the BFI.[45]

The BFI has been validated and used in patients with various conditions, including cancer, osteoarthritis, and rheumatoid arthritis.[12] The construct validity, concurrent validity, and discriminant validity of BFI have been demonstrated in cancer patients. Reliability of the BFI was assessed based on one study that included 305 adult patients with cancer (coefficient alphas were 0.95 to 0.96).[44] An MCID for the BFI in patients with XLH was not identified in the literature.

Rickets Severity Score

RSS was constructed to measure rickets severity in the wrists and knees based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected.[36,37] RSS is a 10-point scale (4 points for the wrists and 6 points for the knees), where a higher score indicates greater severity of rickets (Table 75). A score of 10 represents the most extreme degree of severity, while a score of 0 indicates the absence of radiographic changes of rickets.[36,37]

The RSS has been validated in patients with nutritional rickets.[37] The radiographic response following treatment of nutritional rickets can be assessed by the RSS, and RSS values correlate with values of serum ALP. The RSS has been used in children with XLH to evaluate the effect of drug therapy. The inter-rater reliability of the RSS was evaluated in Study CL201, which was a phase II, randomized controlled trial of children with XLH. The Pearson correlation ranged from 0.83 to 0.89. The intra-rater reliability was excellent (Pearson correlation = 0.91). In clinical trials of XLH, RSS was found to be statistically significantly correlated with clinical features of XLH, such as growth, walking ability, and self-reported pain and physical function.[37] In addition, patients who had a baseline RSS greater than or equal to 1.5 had severely compromised bone health, with higher levels of ALP and greater impairments in clinical outcomes, compared with patients who had a baseline RSS of less than 1.5.[37] An MCID for RSS was not identified from the literature.

Table 75: 10-Point Radiographic Scoring Method for Rickets

Wrist: score both radius and ulna separately (score for worst wrist)		
	Grade	Radiographic features
	0	Normal growth plate without changes of rickets
	0.5	Lucency of metaphyseal margin without fraying or irregularity
	1	Widened growth plate and irregular metaphyseal margin, but without concave cupping
	1.5	Partial metaphyseal concavity or incomplete fraying of metaphyseal margin
	2	Metaphyseal concavity with fraying of margins
Bones × 2 points = 4 points possible		
Knee: score both femur and tibia separately (score for worst knee)		
Multiply the grade in A by the multiplier in B for each bone, then add femur and tibia scores together.		
A	Grade	Degree of lucency and widening of zone of provisional calcification
	0	Normal growth plate without changes of rickets
	1	Partial lucency, smooth margin of metaphysis visible
	2	Partial lucency, smooth margin of metaphysis NOT visible
	3	Complete lucency, epiphysis appears widely separated from distal met
B	Multiplier	Portion of growth plate affected
	0.5	≤ 1 condyle or plateau
	1	2 condyles or plateaus
2 bones × 1 point × 3 points = 6 points possible		
Total: 10 points possible		

Source: Thacher et al. (2000).[36]

Radiographic Global Impression of Change

The RGI-C scale was constructed as a complement to the RSS to measure the change in severity of rickets.[38] The RGI-C methodology allows for the evaluation of change in the radiographic appearance of rickets through a side-by-side comparison of an earlier image and an image taken at a later time point.[10] It has been validated in patients with hypophosphatasia.[38] It is a 7-point change scale that provides an assessment of bone structure associated with the pathophysiology of hypophosphatasia. Change from baseline in RGI-C is based on ratings of the characteristics of severe hypophosphatasia, including irregularity of the provisional zone of calcification; physeal widening; metaphyseal flaring, fraying, radiolucencies, and patchy osteosclerosis; altered ratio of mid-diaphyseal cortex-to-bone thickness; gracile bones; absence of some or all bones; and recent fractures. For patients with rickets, a reduction of 3 points (recorded as "–3") represents severe worsening, while an increase of 3 points (recorded as "+3) indicates complete healing of the skeletal disease (Table 76). For each patient, the mean score among the radiologists was used for analysis, with a response to treatment defined as a mean increase of 2 or more points (i.e., substantial healing).

Table 76: Scores on the Radiographic Global Impression of Change and Clinical Interpretation

Rating	Clinical interpretation
–3	Very much worse (severe worsening of rickets)
–2	Much worse (moderate worsening of rickets)
–1	Minimally worse (minimal worsening of rickets)
0	Unchanged
+1	Minimally better (minimal healing of rickets)
+2	Much better (substantial healing of rickets)
+3	Very much better (complete or near complete healing of rickets)

Source: Clinical Study Report for Study CL201.[10]

Inter-rater agreement was evaluated among pediatric radiologists in pediatric patients with hypophosphatasia. Good to moderate intra- and inter-rater agreement was achieved. The RGI-C score was found to be significantly associated with the RSS and with measures of global function, disability, endurance, and growth in patients aged six years to 12 years at baseline.[38] An MCID for the RGI-C was not identified in the literature.

Western Ontario and McMaster Universities Osteoarthritis Index

The WOMAC is a self-administered questionnaire assessing pain, stiffness, and physical functioning in patients with hip and knee osteoarthritis. It is a valid, reliable, and responsive measure of outcome in knee osteoarthritis[46-48] and has been widely used in other painful musculoskeletal disorders, such as lower back pain, rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia.[49] The WOMAC consists of 24 items divided into three subscales:[50]

- pain (five items): during walking, using stairs, in bed, sitting or lying, and standing upright
- stiffness (two items): after first waking and later in the day
- physical function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in/out of a car, shopping, putting on/taking off socks, rising from bed, lying in bed, getting into/out of a bath, sitting, getting on/off toilet, heavy domestic duties, light domestic duties.

There are two scale formats for the WOMAC: a 10 cm VAS and a 5-point Likert scale. The two formats were found to be highly correlated and to yield similar precision for discriminating treatments in patients with osteoarthritis.[51] The Likert version of the WOMAC was used in Study CL303. It is rated on an ordinal scale of 0 to 4, where 0 means the lowest level of symptoms or physical disability. Each subscale is summated to a maximum score of 20, 8, and 68, respectively, providing a maximum global score of 96 (the sum of the three subscales).[52] Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

One study suggests that the WOMAC has acceptable face and content validity in the adult XLH population.[49] Another study that enrolled adult patients with XLH also tested the scale discriminant validity and convergent-divergent validity and supported the use of the WOMAC in this study population.[72] An MCID for improvement or worsening was not identified for the Likert format of the WOMAC. An MCID for improvement ranging from 0.80 points to 1.01 points was reported for the WOMAC VAS scale in patients with osteoarthritis,

reflecting changes of 17% to 22% of baseline scores. An MCID for worsening conditions ranging from 0.29 points (6%) to 1.03 points (22%) was also reported for the VAS scale.[73]

6-Minute Walk Test

The 6MWT is a supervised test that measures the distance a patient can walk on a hard, flat surface over a six-minute period.[54] A specific protocol outlining training, level of support provided to the patient, and standardization of distance available for the patient to walk (30 m) is provided by the American Thoracic Society.[54]

The 6MWT has been used and validated in multiple adult patient populations with cardiopulmonary conditions (e.g., heart failure, chronic obstructive pulmonary disease, pulmonary hypertension).[54] Multiple studies have also established a proposed MCID in these populations. Reported distances associated with a noticeable functional improvement range from 54 m in patients with stable chronic obstructive pulmonary disease and 43 m in patients with heart failure.[54] It should be noted that patients in these populations are significantly older than the majority of adult patients enrolled in the pivotal studies in this review. Initial improvements in 6MWT results should be interpreted with caution, given that there has been a well-documented learning effect in patients previously unfamiliar with the test.[67] Motivation, encouragement, and co-operation can have a significant positive impact on the results, and the magnitude of these effects could be comparable to the effect of interventions.[68,69] This could be of special concern in situations where blinding is not present or is compromised, particularly when no comparator arm is available.

A systematic review of the literature on the 6MWT in the pediatric population across nine conditions, including those with musculoskeletal disorders, identified several issues associated with use of the test in this population.[55] MCID values reported in the systematic review ranged from 36 m in patients with spina bifida to 68 m in obese patients. Other studies have found that the age, height, and weight of a child can have an impact on the distance travelled in six minutes. This may have an impact on 6MWT results obtained from trials of longer duration.[56] The reliability and validity of the 6MWT were evaluated in 24 patients with hypophosphatasia. The test-retest reliability was high for children, adolescents, and adults (i.e., Pearson's correlation coefficients ranged from 0.81 to 0.95).[57] MCIDs for patients with hypophosphatasia were estimated using distribution-based methods (31 m for children and adults and 43 m for adolescents).[57]

Pediatric Orthopaedic Society of North America – Pediatric Outcomes Data Collection Instrument

PODCI is a self-reported generic measure for children (aged two years to 18 years) with chronic health disorders, specifically any problems related to bone and muscle conditions.[59] PODCI was designed to evaluate overall health, pain, and ability to participate in normal daily activities, as well as more vigorous activities typically associated with young people. It includes a pediatric version to be completed by a parent and an adolescent version that can be completed by the parent, child, or both. It contains five scales that provide a broad view of the physical, mental, and psychosocial status of the child or adolescent patient. The scales evaluate upper extremity and physical function (eight items), transfer and mobility tasks (11 items), sports and physical functioning (21 items), pain and comfort (three items), treatment expectations, happiness (five items), and satisfaction with symptoms. A global functioning scale consists of the mean of the "mean of items" values for the first four scales. Most items use a categorical scale, with a range of three to six choices; some items require respondents to circle "yes" to all responses that apply to the patient. The majority of items

are scored using a 1 to 5 range, with 1 indicating the most positive response (i.e., the activity is easy for the child; the child is very happy; the child never required help from another person). Some items include a sixth response choice, “Child is too young.” These items are coded as missing and removed from the mean score. Subsequently, the raw scores for each scale are converted to a standard score based on the mean of items that make up that scale. All items in a scale are first recalibrated so they are in the same metric, with a range of values from 0 to 5 for each item. Next, the scores for all items comprising a scale are averaged over the number of items answered. The mean of the rescaled values is then multiplied by a constant so each scale has a final range of values between 0 and 100.[59] To make the standard scores comparative across various scales, data from the general US population were transformed for each scale so the normative score for each scale has a mean of 50 and an SD of 10. Thus, a patient scoring above 50 on a particular scale is above the general, healthy population's average, while a patient scoring below 50 on a scale is below the general, healthy population's average. In PODCI, higher scores represent less disability and better functioning.

The psychometric properties of PODCI have been examined. For convergent validity, physician ratings of global function were moderately to highly correlated to parent and adolescent ratings of global function (r = 0.76), upper extremity function (r = 0.62), and transfers and mobility (r = 0.75). For divergent validity, physician ratings of patients' function and severity of diagnosis were not correlated to parent or adolescent ratings of comfort, happiness, or expectations. This instrument was considered to have excellent internal consistency (alpha = 0.76 to 0.95) and parent test-retest reliability (Pearson correlations ranged from 0.71 to 0.97), but poor inter-rater agreement for parent and adolescent responses on all scales.[59] In general, adolescents rated themselves higher than their parents did on every measure of physical and mental health, while parents had higher expectations for treatment outcome, suggesting that many parent and adolescent pairs differed significantly in their assessment of the child's condition. Another analysis of children with cerebral palsy also indicated that the PODCI had high-moderate-to-good test-retest reliability, but variable inter-rater reliability for subjective domains.[74] Concurrent validity was inconsistent across studies. Responsiveness in this population was inconclusive. An MCID for the PODCI was not identified for patients with XLH.

Osteoid Volume/Bone Volume

Osteomalacia is a bone disorder. It is characterized by decreased mineralization of newly formed osteoid at sites of bone turnover.[75] Bone histomorphometry assessment is the most accurate way to diagnose osteomalacia, and is performed through transiliac crest bone biopsy with double tetracycline labelling. Patients diagnosed with osteomalacia show prolonged mineralization lag time and excess osteoid (unmineralized bone matrix) accumulation. Bone volume and osteoid volume are the primary measurements in bone histomorphometry.

In Study CL304, osteoid volume was measured as a percentage of total bone volume (OV/BV).[65] This also referred to the amount of unmineralized osteoid relative to the total amount of mineralized and unmineralized bone. This is a static formation parameter. The reference range of OV/BV is 0.30% to 3.1% in healthy post-menopausal women.[65] A decrease from baseline OV/BV at study end points indicates improvement in osteomalacia at the tissue level. There is no information regarding the validation of OV/BV in the target population. An MCID for change in OV/BV was not identified in the literature.

Short Form (10) for Children Health Survey

The SF-10 is a parent-completed questionnaire intended to assess the health status of children aged five years to 18 years.[61] It is part of the Quality Metric Pediatric Health Surveys and was adapted from the Child Health Questionnaire. The SF-10 contains 10 Likert-type scale items (graded using 4- and 5-point responses) that use a four-week recall period and yield baseline physical and psychosocial health summary scores on the following physical and psychosocial concepts: physical functioning, role/social physical, general health perceptions, bodily pain, role/social emotional-behavioural, self-esteem, mental health, and general behaviour. There is evidence supporting the reliability, validity, and discriminating ability of the SF-10 in the general US population of children with or without a chronic condition or disability. The summary measures were internally consistent across groups with and without disability. (For physical summary scores, Cronbach's alpha = 0.78 and 0.76; for psychosocial summary scores, Cronbach's alpha = 0.80 and 0.72.) No data regarding its responsiveness are available.[61,62] An MCID for the SF-10 was not specified in children with XLH.

The Bruininks-Oseretsky Test of Motor Proficiency – Second Edition

The BOT-2 is intended for use by practitioners and researchers as a discriminative and evaluative measure to characterize motor performance, specifically in the areas of fine manual control, manual coordination, body coordination, and strength and agility.[60] It is an instrument that measures fine and gross motor skills in individuals four years to 21 years of age. Each of its four areas are broken up into two subtest areas. The BOT-2 is a norm-referenced test in that it has standardized test procedures that allow for the collection of data on a variety of motor ability tests, and compares these data to those of the referenced standards.[76] In Study CL201, BOT-2 was used to generate a a composite score from two subtests: running speed and agility, and strength.[10] The running speed and agility subtest measures a shuttle run, sideways stepping over a balance beam, a one-legged stationary hop, a one-legged side hop, and a two-legged side hop. The maximum score for the running speed and agility subtest is 52. The components of the strength subtest are standing long jump, knee or full push-ups, sit-ups, wall sit, and V-up. The maximum score for this subtest is 42.

The raw score for each item is converted into a point score. The point scores for all of the items in each subtest are summed to get the total point scores for the BOT-2. An increase in the total point scores represents an improvement.

The reliability of the BOT-2 was evaluated in children between the ages of four years and 21 years. The inter-rater reliability was found to be greater than 0.90, except in the fine motor precision subtest (r = 0.86). Test-retest reliability was also examined in children of different age groups (four years to seven years, eight years to 12 years, and 13 years to 21 years), with all correlation coefficients greater than or equal to 0.90 for the Total Motor Composite.[77] No evidence of an MCID of BOT-2 was identified.

PROMIS Scores for Pediatric Pain Interference, Fatigue, and Physical Function Mobility Scales

The PROMIS is a set of measures covering different domains of physical, mental, and social health.[58] It contains a bank of questions from which relevant items can be extracted and used to create a custom form. At present, PROMIS assesses 51 distinct health domains for adults and 18 distinct health domains for the pediatric population. The PROMIS relies on large collections of items (item banks) for each individual health domain. Item

banks are calibrated using modern psychometric techniques, including item response therapy, which ensures that they can be administered flexibly while remaining directly comparable: PROMIS measures can be delivered as a fixed-length short form, or as an individually tailored computerized adaptive test (CAT), where questions from the item bank are sequentially presented to patients using an algorithm that ensures only the more relevant and informative questions are asked. The PROMIS calibration method also allows scores to be directly compared with reference populations and other patient-reported outcomes that measure the same domains. A key aim of PROMIS was to standardized the outcome measurement in clinical practice and research, analogous to more commonly regarded health measurements, thereby facilitating comparability of data across studies and settings.[58] The output from a PROMIS score is a t score, which is a standardized score developed using a representative sample of the entire population. The t score has a mean of 50 and an SD of 10 in that population. The t scores were generated for each domain based on the questions included for scoring. Higher scores represent more of what is measured — for example, more mobility, more pain, or more fatigue.[13] Studies performing psychometric evaluations of the PROMIS physical function item bank have suggested that the item bank provides a common metric and can improve the measurement of physical function by facilitating the standardization of patient-reported outcome measures and the implementation of CAT for more efficient physical function assessments over a larger range.[78] Studies evaluating the psychometric properties of the PROMIS pediatric scales have reported that the CAT had limited usefulness over and above what can be accomplished with the existing static evaluating instruments.[79] Studies examining the validity of the PROMIS fatigue item bank indicated that its reliability and validity were acceptable.[80] There is no information available regarding the MCID for the PROMIS domains in various populations.

In Study CL301, PROMIS pain interference, physical function mobility, and fatigue questionnaires were administered to patients aged greater than or equal to five years of age.[13] It is unclear whether a CAT or fixed-length form was used.

Faces Pain Scale – Revised

The FPS is a self-reported measure for evaluating pain intensity in children.[53] It consists of a series of horizontal, gender-neutral faces that depict a neutral facial expression of “no pain” on the left and an expression of “most pain possible” on the right. The FPS has seven faces scoring from 0 to 6, with higher scores indicating more severe pain, while the revised version (FPS-R) has six faces scoring from 0 to 10. Patients are instructed to point to the face that shows how much they hurt. The psychometric properties of the FPS-R were evaluated in a systematic review comparing various faces pain scales that were commonly used for pain intensity in children.[53] In this review, 22 studies enrolled children who had procedural pain or were taking medications for pain management. The number of children ranged from 20 to 620, with ages ranging from one month to 19 years; however, most were four years to 12 years old. The results supported the reliability and validity of the FPS-R for assessing pain intensity in children: the correlation coefficient between the FPS-R and other self-reported pain scales ranged from 0.66 to 0.96. Test-retest reliability was considered adequate. The responsiveness of the FPS-R was also demonstrated. The patients or their parents found the scale easy to use. An MCID has not been specified for the FPS-R.

References

1. Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res.* 2011;26(7):1381-1388.
2. Center for Drug Evaluation Research. Multi-discipline review(s). *Crysvita (burosumab) injection. Company: Ultragenyx Pharmaceutical, Inc. Application No.: 761068. Approval date: 04/17/2018 (FDA approval package)*. Rockville (MD): U. S. Food and Drug Administration (FDA); 2018: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761068Orig1s000TOC.cfm. Accessed 2019 Sep 19.
3. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol.* 2019;15(7):435-455.
4. National Institute for Health and Care Excellence. Burosumab for treating X-linked hypophosphataemia in children and young people. *(Highly specialised technologies guidance HST8)* 2018 https://www.nice.org.uk/guidance/hst8. Accessed 2019 Sep 19.
5. Rafaelsen S, Johansson S, Raeder H, Bjerknes R. Hereditary hypophosphatemia in Norway: a retrospective population-based study of genotypes, phenotypes, and treatment complications. *Eur J Endocrinol.* 2016;174(2):125-136.
6. Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. Incidence and prevalence of nutritional and hereditary rickets in southern Denmark. *Eur J Endocrinol.* 2009;160(3):491-497.
7. Crysvita™ (burosumab injection): 10 mg/mL, 20 mg/mL, 30 mg/mL; solution for subcutaneous injection [product monograph]. Oakville (ON): Innomar Strategies; 2018 Dec 5.
8. Health Canada reviewer's report: Crysvita (burosumab) [CONFIDENTIAL internal report]. Ottawa (ON): Therapeutics Products Directorate, Health Canada; 2018.
9. SickKids. CALIPER reference interval database. 2019; http://www.sickkids.ca/Caliperproject/intervals/index.html. Accessed 2019 Oct 1.
10. Clinical Study Report: CL201. A randomized, open-label, dose finding, phase 2 study to assess the pharmacodynamics and safety of the anti-FGF23 antibody, KRN23, in pediatric patients with X-linked hypophosphatemia (XLH) [CONFIDENTIAL internal sponsor's report]. Novato (CA): Ultragenyx Pharmaceutical Inc.; 2017 May 16.
11. Clinical Study Report: CL205. An open-label, phase 2 study to assess the safety, pharmacodynamics, and efficacy of KRN23 in children from 1 to 4 years old with X-linked hypophosphatemia (XLH) [CONFIDENTIAL internal sponsor's report]. Novato (CA): Ultragenyx Pharmaceutical Inc.; 2017 Oct 5.
12. Clinical Study Report: CL303. A randomized, double-blind,placebo-controlled, phase 3 study with open-label extension to assess the efficacy and safety of KRN23 in adults with X-linked hypophosphatemia (XLH) [CONFIDENTIAL internal sponsor's report]. Novato (CA): Ultragenyx Pharmaceutical Inc.; 2018 Apr 9.
13. Clinical Study Report: CL301. A randomized, open-label, phase 3 study to assess the efficacy and safety of KRN23 versus oral phosphate and active vitamin D treatment in pediatric patients with X-linked hypophosphatemia (XLH) [CONFIDENTIAL internal sponsor's report]. Novato (CA): Ultragenyx Pharmaceutical Inc.; 2019 Feb 13.
14. Bonewald LF, Wacker MJ. FGF23 production by osteocytes. *Pediatr Nephrol.* 2013;28(4):563-568.
15. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect.* 2014;3(1).
16. Hardy DC, Murphy WA, Siegel BA, Reid IR, Whyte MP. X-linked hypophosphatemia in adults: prevalence of skeletal radiographic and scintigraphic features. *Radiology.* 1989;171(2):403-414.
17. Che H, Roux C, Etcheto A, et al. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur J Endocrinol.* 2016;174(3):325-333.
18. Forestier-Zhang L, Watts L, Turner A, et al. Health-related quality of life and a cost-utility simulation of adults in the UK with osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia. *Orphanet J Rare Dis.* 2016;11(1):160.
19. Liu S, Tang W, Zhou J, et al. Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. *J Am Soc Nephrol.* 2006;17(5):1305-1315.
20. Health Canada. Summary basis of decision (SBD) for Crysvita. 2019; https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?lang=en&linkID=SBD00429. Accessed 2019 Sep 19.
21. CDR submission: Crysvita™ (burosumab injection), 10 mg/mL, 20 mg/mL, 30 mg/mL single use 1 mL vials [CONFIDENTIAL sponsor's submission]. Brisbane (CA): Ultragenyx Canada Inc; 2019 Jul 23.
22. ONE-ALPHA® (alfacalcidol): 1 and 0.25 mcg capsules, 2 mcg/mL oral drops, 2 mcg/mL injection, vitamin D analogue [product monograph]. Thornhill (ON): LEO Pharma Inc; 2017 Aug 14: https://pdf.hres.ca/dpd_pm/00040724.PDF. Accessed 2019 Nov 20.
23. CALCITRIOL-ODAN™ (calcitriol): 0.25 mcg and 0.5 mcg capsules [product monograph]. Pointe-Claire (QC): Odan Laboratories Ltd; 2014 Sep 23: https://pdf.hres.ca/dpd_pm/00027408.PDF. Accessed 2019 Sep 23.
24. Sensipar® (cinacalcet hydrochloride): 30 mg, 60 mg, 90 mg tablets [product monograph]. Mississauga(ON): Amgen Canada Inc; 2018 Nov 20: https://pdf.hres.ca/dpd_pm/00048361.PDF. Accessed 2019 Nov 20.

25. Health Canada. Phoslax (sodium phosphate) [natural health product]. 2018 Feb 6; https://health-products.canada.ca/lnhpd-bdpsnh/info.do?licence=80000689. Accessed 2019 Nov 20.

26. Health Canada. Phosphate effervescent tablets (phosphate) [natural health product]. 2017 Apr 19; https://health-products.canada.ca/lnhpd-bdpsnh/info.do?licence=80068758. Accessed 2019 Nov 20.

27. Health Canada. Jamp-Phosphate Effervescent (phosphate) [natural health product]. 2018 Feb 6; https://health-products.canada.ca/lnhpd-bdpsnh/info.do?licence=80036102. Accessed 2019 Nov 20.

28. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.

29. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2019 Aug 12.

30. Imel EA, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial. *Lancet.* 2019;393(10189):2416-2427.

31. Carpenter TO, Whyte MP, Imel EA, et al. Burosumab therapy in children with X-linked hypophosphatemia. *N Engl J Med.* 2018;378(21):1987-1998.

32. Whyte MP, Carpenter TO, Gottesman GS, et al. Efficacy and safety of burosumab in children aged 1-4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. *Lancet Diabetes Endocrinol.* 2019;7(3):189-199.

33. Insogna KL, Briot K, Imel EA, et al. A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: week 24 primary analysis. *J Bone Miner Res.* 2018;33(8):1383-1393.

34. Portale AA, Carpenter TO, Brandi ML, et al. Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calcif Tissue Int.* 2019;105(3):271-284.

35. World Health Organization. WHO child growth standards: training course on child growth assessment. Geneva (CH): World Health Organization; 2008: https://www.who.int/childgrowth/training/module_c_interpreting_indicators.pdf. Accessed 2019 Nov 20.

36. Thacher TD, Fischer PR, Pettifor JM, et al. Radiographic scoring method for the assessment of the severity of nutritional rickets. *J Trop Pediatr.* 2000;46(3):132-139.

37. Thacher TD, Pettifor JM, Tebben PJ, et al. Rickets severity predicts clinical outcomes in children with X-linked hypophosphatemia: Utility of the radiographic Rickets Severity Score. *Bone.* 2019;122:76-81.

38. Whyte MP, Fujita KP, Moseley S, Thompson DD, McAlister WH. Validation of a novel scoring system for changes in skeletal manifestations of hypophosphatasia in newborns, infants, and children: the Radiographic Global Impression of Change scale. *J Bone Miner Res.* 2018;33(5):868-874.

39. Zivicnjak M, Schnabel D, Billing H, et al. Age-related stature and linear body segments in children with X-linked hypophosphatemic rickets. *Pediatr Nephrol.* 2011;26(2):223-231.

40. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat 11.* 2002(246):1-190.

41. Atkinson TM, Mendoza TR, Sit L, et al. The Brief Pain Inventory and its "pain at its worst in the last 24 hours" item: clinical trial endpoint considerations. *Pain Med.* 2010;11(3):337-346.

42. Song CY, Lin SF, Huang CY, et al. Validation of the Brief Pain Inventory in patients with low back pain. *Spine (Phila Pa 1976).* 2016;41(15):E937-942.

43. Mathias SD, Crosby RD, Qian Y, et al. Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form. *J Support Oncol.* 2011;9(2):72-78.

44. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer.* 1999;85(5):1186-1196.

45. Brief Fatigue Inventory. Sydney (AU): The Moving Ahead Centre of Research Excellence (CRE) in Brain Recovery; [Date unknown]: http://movingahead.psy.unsw.edu.au/documents/research/outcome%20measures/adult/TBI%20Related%20Symptoms/Website%20Brief%20Fatigue%20Inventory.pdf. Accessed 2019 Oct 7.

46. Roos EM, Klässbo M, Lohmander LS. WOMAC osteoarthritis index. Reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis. *Scand J Rheumatol.* 1999;28(4):210-215.

47. Salaffi F, Carotti M, Grassi W. Health-related quality of life in patients with hip or knee osteoarthritis: comparison of generic and disease-specific instruments. *Clin Rheumatol.* 2005;24(1):29-37.

48. Brazier JE, Harper R, Munro J, Walters SJ, Snaith ML. Generic and condition-specific outcome measures for people with osteoarthritis of the knee. *Rheumatology (Oxford).* 1999;38(9):870-877.

49. Theodore-Oklota C, Bonner N, Spencer H, et al. Qualitative research to explore the patient experience of X-linked hypophosphatemia and evaluate the suitability of the BPI-SF and WOMAC as clinical trial end points. *Value Health.* 2018;21(8):973-983.

50. Physiopedia. WOMAC Osteoarthritis Index. 2019; https://www.physio-pedia.com/index.php?title=WOMAC_Osteoarthritis_Index&oldid=180346. Accessed 2019 Oct 7.

51. Bolognese JA, Schnitzer TJ, Ehrich EW. Response relationship of VAS and Likert scales in osteoarthritis efficacy measurement. *Osteoarthritis Cartilage.* 2003;11 (7):499-507.

52. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Rheum.* 2001;45(5):453-461.

53. Tomlinson D, von Baeyer CL, Stinson JN, Sung L. A systematic review of faces scales for the self-report of pain intensity in children. *Pediatrics.* 2010;126(5):e1168-1198.

54. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166:111-117.

55. Bartels B, de Groot JF, Terwee CB. The six-minute walk test in chronic pediatric conditions: a systematic review of measurement properties. *Phys Ther.* 2013;93(4):529-541.

56. Priesnitz CV, Rodrigues GH, Stumpf Cda S, et al. Reference values for the 6-min walk test in healthy children aged 6-12 years. *Pediatr Pulmonol.* 2009;44(12):1174-1179.

57. Phillips D, Tomazos IC, Moseley S, et al. Reliability and validity of the 6-minute walk test in hypophosphatasia. *JBMR Plus.* 2019;3(6):e10131.

58. Evans JP, Smith A, Gibbons C, Alonso J, Valderas JM. The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS): a view from the UK. *Patient Relat Outcome Meas.* 2018;9:345-352.

59. Klepper SE. Measures of pediatric function: Child Health Assessment Questionnaire (C-HAQ), Juvenile Arthritis Functional Assessment Scale (JAFAS), Pediatric Outcomes Data Collection Instrument (PODCI), and Activities Scale for Kids (ASK). *Arthritis Care Res (Hoboken).* 2011;63(Suppl 11):S371-382.

60. Deitz JC, Kartin D, Kopp K. Review of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2). *Phys Occup Ther Pediatr.* 2007;27(4):87-102.

61. Williams VSL, Soliman AM, Barrett AM, Klein KO. Review and evaluation of patient-centered psychosocial assessments for children with central precocious puberty or early puberty. *J Pediatr Endocrinol Metab.* 2018;31(5):485-495.

62. Saris-Baglama RN, DeRosa MA, Raczek AE, Ware JE. Preliminary validation of the SF-10v2 for Children among those with and without disabilities. Presented at: APHA 134th Annual Meetiong and Exposition; 2006 Nov 4-8; Boston, Massachusetts. 2006; https://apha.confex.com/apha/134am/techprogram/paper_134676.htm. Accessed 2019 Oct 7.

63. Geiger R, Strasak A, Treml B, et al. Six-minute walk test in children and adolescents. *J Pediatr.* 2007;150(4):395-399, 399.e391-392.

64. Insogna KL, Rauch F, Kamenicky P, et al. Burosumab improved histomorphometric measures of osteomalacia in adults with X-linked hypophosphatemia: a phase 3, single-arm, international trial. *J Bone Miner Res.* 2019.

65. Clinical Study Report: CL304. An open-label, single-arm, phase 3 study to evaluate the effects of KRN23 on osteomalacia in adults with X-lined hypophosphatemia (XLH) [CONFIDENTIAL internal sponsor's report]. Novato (CA): Ultragenyx Pharmaceutical Inc.; 2018 Aug 27.

66. Clinical Study Report: CL201 extension. A randomized, open-label, dose finding, phase 2 study to assess the pharmacodynamics and safety of the anti-FGF23 antibody, KRN23, in pediatric patients with X-linked hypophosphatemia (XLH) [CONFIDENTIAL internal sponsor's report]. Novato (CA): Ultragenyx Pharmaceutical Inc.; 2019 Apr 5.

67. Pankoff BA, Overend TJ, Lucy SD, White KP. Reliability of the six-minute walk test in people with fibromyalgia. *Arthritis Care Res.* 2000;13(5):291-295.

68. Garofano RP, Barst RJ. Exercise testing in children with primary pulmonary hypertension. *Pediatr Cardiol.* 1999;20(1):61-64.

69. Guyatt G, Pugsley SO, Sullivan MJ, et al. Effect of encouragement on walking test performance. *Thorax.* 1984;39(11):818-822.

70. Ultragenyx Canada Inc. response to September 5, 2019 request for additional information regarding Crysvita (burosumab) review: the subgroup analysis for CL303 [CONFIDENTIAL additional sponsor's information]. Brisbane (CA): Ultragenyx Canada Inc.; 2019 Sep 12.

71. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain.* 2005;113(1-2):9-19.

72. Ruppe MD, Zhang X, Imel EA, et al. Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia. *Bone Rep.* 2016;5:158-162.

73. Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. *J Rheumatol.* 2002;29(1):131-138.

74. Harvey A, Robin J, Morris ME, Graham HK, Baker R. A systematic review of measures of activity limitation for children with cerebral palsy. *Dev Med Child Neurol.* 2008;50(3):190-198.

75. Cohen A, Drake MT. Clinical manifestations, diagnosis, and treatment of osteomalacia. In: Post TW, ed. *UptoDate*. Waltham (MA): UpToDate; 2019: www.uptodate.com. Accessed 2019 Nov 20.

76. Bruininks RH, Bruininks BD. Bruininks-Oseretsky Test of Motor Proficiency (BOT-2). 2005.

77. Griffiths A, Toovey R, Morgan PE, Spittle AJ. Psychometric properties of gross motor assessment tools for children: a systematic review. *BMJ Open.* 2018;8(10):e021734.

78. Rose M, Bjorner JB, Gandek B, et al. The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. *J Clin Epidemiol.* 2014;67(5):516-526.

79. Varni JW, Magnus B, Stucky BD, et al. Psychometric properties of the PROMIS (R) pediatric scales: precision, stability, and comparison of different scoring and administration options. *Qual Life Res.* 2014;23(4):1233-1243.

80. Ameringer S, Elswick RK, Jr., Menzies V, et al. Psychometric evaluation of the Patient-Reported Outcomes Measurement Information System Fatigue-Short Form across diverse populations. *Nurs Res.* 2016;65(4):279-289.