

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761068Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

MULTI-DISCIPLINARY REVIEW

Application Type	BLA
Application Number(s)	761068
Priority or Standard	Priority
Submit Date(s)	8/17/2017
Received Date(s)	8/17/2017
PDUFA Goal Date	4/17/2018
Division/Office	Division of Bone, Reproductive and Urologic Products/ Office of Drug Evaluation III
Review Completion Date	4/5/2018
Established/Proper Name	Burosumab
(Proposed) Trade Name	Crysvita
Applicant	Ultragenyx Pharmaceutical Inc.
Dosage Form(s)	10, 20 and 30 mg/mL solution for injection in single-dose vial
Applicant Proposed Dosing Regimen(s)	<u>Pediatric</u> : 0.8 mg/kg SC Q2 weeks (starting dose; titration to max 2.0 mg/kg Q2weeks based on serum phosphorus; minimum dose 10 mg, maximum dose 90 mg) <u>Adult</u> : 1 mg/kg SC Q4 weeks, maximum dose 90 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older
Recommendation on Regulatory Action	Approval for both adult and pediatric patients
Recommended Indication(s)/Population(s) (if applicable)	Treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older

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OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 DPMH = Division of Maternal and Pediatric Health
 PLLR = Pregnancy and lactation labeling
 COA = Clinical Outcomes Assessment Staff
 OSI=Office of Scientific Investigations
 OSIS = Office of Study Integrity and Surveillance
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

Glossary

AC	Advisory Committee
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AR	Adverse Reaction
AUC	Area Under the Curve
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BPI	Brief Pain Inventory
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
COA	Clinical Outcomes Assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Clinical Review Template
CSR	Clinical Study Report
CSS	Controlled Substance Staff
DBRUP	Division of Bone, Reproductive and Urologic Products
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCTD	electronic Common Technical Document
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FGF23	Fibroblast growth factor-23
GCP	Good Clinical Practice
GRMP	Good Review Management Practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent To Treat

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MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent To Treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	New Molecular Entity
OCS	Office of Computational Science
ODE	Office of Drug Evaluation
OND	Office of New Drugs
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PI	Prescribing Information or Package Insert
PK	pPharmacokinetics
PMC	PostMarketing Commitment
PMR	PostMarketing Requirement
PP	Per Protocol
PPI	Patient Package Insert
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update report
REMS	Risk Evaluation and Mitigation Strategy
RGI-C	Radiographic Impression of Change
RSS	Rickets Severity Score
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGE	Special Government Employee
SOC	Standard of Care
TEAE	Treatment Emergent Adverse Event
WOMAC	Western Ontario and McMaster Universities Arthritis Index
XLH	X-linked Hypophosphatemia

1. Executive Summary

1.1. Product Introduction

Ultragenyx Pharmaceuticals, Inc., has submitted this Biologic Licensing Application for burosumab (CRYSVITA) for the treatment of X-linked hypophosphatemia (XLH). Burosumab, a first -in-class biologic agent, is a human monoclonal antibody that inhibits the function of fibroblast growth factor 23 (FGF23), an endocrine factor that regulates phosphate homeostasis and vitamin D metabolism. Excess FGF23 causes the disease XLH. CRYSVITA is proposed for the indication of treatment of XLH in adult and pediatric patients 1 year of age and older.

CRYSVITA is administered by subcutaneous injection. The proposed starting dose for pediatric patients (age 1 to <18 years old) is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every 2 weeks; based on serum phosphorus levels, the dose may be titrated up to 2.0 mg/kg. The proposed dose for adult patients (\geq age 18 years old) is 1.0 mg/kg, rounded to the nearest 10 mg, administered every 4 weeks. The maximum dose for any patient, pediatric or adult, is 90 mg. CRYSVITA is supplied as a 10 mg/mL, 20 mg/mL or 30 mg/mL solution in single-use vials.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness as required by statute to support approval of burosumab in the treatment of XLH in adult and pediatric patients age \geq 1 year. In studies of children with XLH age 1-12 years of age, burosumab is associated with consistent increases in serum phosphorus, and significant improvement in radiographic rickets scores and serum alkaline phosphatase. These changes are expected to result in substantial improvements in long-term clinical outcomes of growth and skeletal deformities. In studies of adults with XLH (age \geq 18 - 65 years), burosumab is associated with significant increases in serum phosphorus and improvements in osteomalacia, as shown by improved healing of pseudofractures and fractures compared to placebo, and reduction of bone histomorphometric parameters of osteomalacia. Although adolescents with XLH (age 13-17 years inclusive) have not been studied, the disease process and response to therapy in this population are expected to be similar to that of young children with XLH and open epiphyseal plates. Therefore, it is reasonable to extrapolate pediatric and adult efficacy to the adolescent population.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

X-linked hypophosphatemia (XLH) is caused by inactivating mutations in the PHEX gene resulting in excessive fibroblast growth factor-23 (FGF23) production by osteocytes. FGF23 is a key regulator of phosphate and vitamin D metabolism. Excess FGF23 causes renal phosphate wasting and reduced production of active vitamin D (1, 25 dihydroxyvitamin D). The resultant hypophosphatemia in XLH leads to inadequate skeletal mineralization, i.e. rickets and osteomalacia. XLH is a rare disease that affects approximately 1/20,000 live births, with an estimated prevalence of 3,000 pediatric and 12,000 adult patients in the U.S. Most patients with XLH are diagnosed in early childhood with leg bowing after beginning to walk, or because of a family history. Most children experience gait abnormalities, lower extremity pain and short stature. XLH is a serious disease that irreversibly impairs growth and development of the skeleton in childhood and adolescence, and continues to interfere with normal bone mineralization throughout life. XLH differs from other forms of rickets and osteomalacia in that treatment with Vitamin D is not effective (vitamin D resistant rickets).

There are no approved therapies for treatment of XLH. Most children with the disease are treated, from the time of diagnosis until growth stops, with oral supplements of phosphate (4 times daily) and active vitamin D analogs. The concerns with this conventional therapy include tolerability and compliance, mineralization of tissues outside bone, especially kidneys (nephrocalcinosis), and hyperparathyroidism which may require surgery. Frequent monitoring is needed to manage these serious long-term safety concerns. In addition, conventional therapy does not completely correct bone deformities and impaired growth.

Substantial evidence of effectiveness for burosumab was demonstrated in four clinical studies. There were two adult studies (CL303 and CL304) and two pediatric studies (CL201 and CL205). In adult subjects, trial CL303 is a randomized, double blind, placebo controlled study in 134 patients with XLH who had a serum phosphorus less than 2.5 mg/dL and skeletal pain at baseline. Study CL304 is an open label single arm bone biopsy study that enrolled 14 adult patients with XLH and a baseline serum phosphorus less than 2.5 mg/dL. Subjects in the adult studies received 1mg/kg burosumab (rounded to the nearest 10 mg) every 4 weeks. The dose was reduced if hyperphosphatemia occurred. Study CL201 is an open label, single arm study in pediatric subjects with XLH age 5 – 12 years. The study evaluated starting dose of 0.1, 0.2 or 0.3 mg/kg every two weeks or 0.2, 0.4 or 0.6 mg/kg every four weeks with titration based on serum phosphorus level. Study CL205 is an open label, single arm study in 10 pediatric subjects with XLH age 1 – 4 years. All patients were treated with a starting dose of burosumab 0.8 mg/kg every 2 weeks with titration based on serum phosphorus level. The pediatric studies did not have a control group for ethical reasons. A retrospective natural history study was conducted in children age 5 – 14 years. Radiographs for the natural history study and the pediatric treatment trials were intermingled and read by the same blinded radiologists.

In adults, the primary endpoint of the placebo-controlled trial (CL303) is the proportion of subjects who achieve serum phosphorus above the lower level of the normal range at 2 weeks post dose. Once a month burosumab dosing achieved normal phosphorus levels in 94% of subjects compared to 8% of placebo treated subjects. Secondary endpoints included change from baseline in worst pain by the Brief Pain Inventory (BPI). Improving trends in pain were seen but did not reach statistical significance. Radiologic evidence of osteomalacia-related fracture and pseudofracture healing was a secondary endpoint. Among

subjects with such lesions at baseline, healing at week 24 occurred in 50% of burosumab treated subjects compared to 13% of placebo treated subjects. In a separate bone biopsy study in adults (CL304), treatment with burosumab resulted in decreases in osteomalacia related indices including a 57% reduction in osteoid volume/bone volume, a 33% reduction in osteoid thickness and a 74% reduction in mineralization lag time. This study did not have a control group but it is not anticipated that bone mineralization would resolve spontaneously in XLH patients. In children, for study CL201, the primary pharmacodynamic endpoint was serum phosphorus. The primary clinical endpoint was change from baseline in total rickets severity score (RSS) with the radiographic impression of change (RGIC) used as a secondary endpoint. In children aged 1-4 years, for study CL205, the primary efficacy endpoint was change from baseline in serum phosphorus level. Secondary endpoints included change from baseline in RSS and RGIC. A more stable serum phosphorus level was seen with burosumab administered every 2 weeks when compared to burosumab administered every 4 weeks with a mean increase from a baseline of 2.4 mg/dL to 3.3 mg/dL. In study CL 205 all subjects reached a serum phosphorus level within the normal range. Radiologic rickets severity scores (RSS) decreased a mean of 59% from baseline at week 40 in children age 1-4 years, and a decrease of 55% from baseline was observed in older children age 5-12 years. Radiographic global impression of change (RGIC) scores at week 40 improved 2.3 points on a 3-point scale in children 1-4 years and 1.7 points in children age 5-12 years. In the retrospective natural history study, the RSS decreased 12% and the RGI-C increased 0.8 points on the 3-point scale. Comparison of the results of the natural history study and the pediatric treatment trials provide support for the effectiveness of burosumab therapy in the pediatric population.

The safety database for burosumab included a total of 175 adults and 65 children with XLH who received at least one dose of burosumab. Except for the adult placebo controlled trial, the submitted burosumab studies were open-label and uncontrolled. The mean duration of burosumab exposure was 45 weeks in 1-5 years olds, 123 weeks in 5-12 year olds, and 48 weeks in adults. There were no deaths in any of the XLH studies. Two serious adverse events (one pyrexia and myalgia, and one tooth abscess) occurred in children. Both events resolved with therapeutic intervention and burosumab was continued. In adults, serious adverse events were reported in 3% of placebo and 3% of burosumab treated subjects in the placebo controlled trial (24 weeks). No subjects discontinued treatment. No subjects in the pediatric or phase 3 adult trials withdrew from the studies due to adverse events. Adverse events of concern that were followed closely include hyperphosphatemia and the potential for ectopic mineralization including nephrocalcinosis that can occur in the setting of hyperphosphatemia. Because of the concern for hyperphosphatemia, use of phosphate supplements and active vitamin D is contraindicated with burosumab use and the burosumab dose is titrated to maintain phosphorus levels in the normal range for age. In the pediatric studies, 3 of the 65 patients (4.6%) required dose reduction for high-normal serum phosphorus levels. In the adult placebo-controlled study, 8 of the 134 patients (6.0%) required dose reduction. Nephrocalcinosis (abnormal mineralization in kidneys) was evaluated by renal ultrasound using a 4-point scale. In the placebo-controlled adult study, small changes (1 point) were seen in both the placebo and the burosumab group with equivalent distribution. In pediatric subjects, 69% of patients had no change in the nephrocalcinosis score, 25% had small increases in score (1 point) and 6% had a small decrease in score (1 point). Ectopic mineralization in the heart was also evaluated by echocardiogram. No significant changes were seen in the echocardiogram evaluations. Renal toxicity is an important consideration with burosumab therapy as it may result from nephrocalcinosis and also because of the concern regarding antibody dependent cellular toxicity targeting renal tubules. No change in renal function was observed in the burosumab studies. Hyperparathyroidism can also be a consequence of hyperphosphatemia. There is no evidence of increase in serum PTH caused by burosumab. Two cases of autonomous parathyroid function were seen in the burosumab pediatric safety database and were likely due to prior phosphate therapy. Injection site reactions occurred in 12% of adults and

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58% of children treated with burosumab. Most cases were mild in severity. Hypersensitivity reactions, generally mild, occurred in 39% of pediatric subjects and 12% of adult subjects exposed to burosumab. One serious reaction of angioedema was most likely attributable to a concomitant medication (lisinopril). Spinal stenosis is a known complication of XLH, mainly due to calcification of the spinal ligaments (enthesopathy). In the burosumab adult trials, 6 patients underwent surgical intervention for spinal stenosis. The role of burosumab therapy in the worsening of spinal stenosis in XLH patients is unclear; this potential for worsening spinal stenosis will be assessed in the postmarketing setting. Restless leg syndrome occurs in XLH patients and has been attributed to changes in serum phosphorus. In the adult placebo controlled trial, 12% of the burosumab treated patients and 8% of placebo treated patients had restless leg syndrome symptoms. No pediatric patients had restless leg symptoms.

The available safety and efficacy data support the approval of Crysvisa (burosumab-twza) for the treatment of XLH in patients 1 year of age or older. A postmarketing study is required to further evaluate concerns for ectopic mineralization, the potential for renal toxicity and the potential for exacerbation of spinal stenosis. The applicant has agreed to add these safety endpoints to their disease monitoring program which will follow XLH patients, both treated and untreated, for 10 years.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> • XLH affects 1 in 20,000 people • Renal phosphate wasting and impaired vitamin D metabolism cause hypophosphatemia and impaired mineralization of bone: rickets (children) and osteomalacia (children and adults) • Symptoms usually begin in early childhood: growth delay; lower limb deformities (usually bowing of femur/tibia, less commonly knock-knees); gait difficulty • Sequelae of childhood rickets: short stature; malalignment of joints leads to early osteoarthritis; surgery may be required to correct deformities • Most adults have persistent hypophosphatemia and osteomalacia, which may cause pseudo-fractures of poorly mineralized bone • Many adults have chronic pain, stiffness, fatigue and/or functional impairment • Enthesopathy (calcification of ligaments and tendons) occurs in most older adults; mechanism is unclear • Tooth abscesses are common in children and adults, attributed to poorly mineralized dentin 	<p>XLH is a serious disease that irreversibly impairs growth and development of the skeleton in childhood and adolescence, and continues to interfere with normal bone mineralization throughout life. Many affected patients have symptoms that are severe or disabling.</p>
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> • There are no approved therapies for XLH • Conventional therapy = oral phosphate supplements + active vitamin D analog (typically calcitriol); doses are not standardized • Phosphate must be taken 3-5 times every day because of rapid excretion in urine, and commonly causes GI upset; compliance is variable • Safety concerns with oral phosphate and active vitamin D: hyperphosphatemia leading to mineralization of tissues outside bone, especially kidneys (nephrocalcinosis); hyperparathyroidism may require surgery • Frequent lab monitoring is required to minimize these risks; dose adjustments may be needed • Most patients are treated throughout childhood until growth stops; many adults are not treated because of uncertain benefits and continued safety concerns 	<p>Current conventional therapy has major drawbacks: inconvenience; tolerability and compliance issues; frequent monitoring needed to manage serious long-term safety concerns; and limited efficacy. Better therapies are urgently needed.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> Efficacy of conventional therapy is difficult to measure because of a lack of controlled studies, but is clearly limited: hypophosphatemia is not fully corrected by oral phosphate and active vitamin D treatment, and most patients have continued short stature and deformities e.g. lower-limb bowing 	
<p>Benefit</p>	<p><u>Pediatric XLH</u></p> <ul style="list-style-type: none"> Efficacy was established in two phase 2 trials of burosumab in a total of 65 children with XLH and bone disease, age 1-12 years; almost all had been receiving conventional therapy prior to enrollment All patients received burosumab (dose titrated according to serum phosphorus level) with no control groups, but some historical data were useful for comparison Efficacy endpoints in children: <ul style="list-style-type: none"> Serum phosphorus, change from baseline Rickets Severity Score (RSS): Radiographic index of rickets features in growth plates/ metaphyses of knee/wrist; graded from 0 (no rickets) to 10 (worst possible) Radiographic Global Impression of Change (RGI-C): Another radiographic score based on changes over time in various rickets features; graded from -3 (severe worsening) to +3 (complete or near complete healing) Growth: Height Z-score (age-/gender-normalized) Serum alkaline phosphatase, an indicator of rickets activity, change from baseline Results: Serum phosphorus and rickets scores (RSS and RGI-C) improved significantly in older and younger children treated with burosumab (table); changes in height Z-score and in leg deformities (e.g. bowing) were small and inconclusive, and probably require longer follow-up 	<p><u>Pediatric XLH</u></p> <p>Most patients in these pediatric studies reached and maintained normal serum phosphorus levels and showed substantial improvement in rickets. In contrast, current conventional therapy does not achieve normal serum phosphorus. As shown in the baseline data, conventional therapy also does not correct rickets, growth delay or bone deformities. Hypophosphatemia and rickets are the underlying cause of all, or nearly all, of the skeletal disease in XLH. Therefore, the study results suggest that treatment with burosumab will yield improved long-term outcomes for bone growth and correction of deformities in children with XLH, especially if treatment is started at a very young age. This may be confirmed in longer-term follow-up studies.</p>

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Dimension	Evidence and Uncertainties			Conclusions and Reasons
		Study CL201	Study CL205	
	Number of patients enrolled	52*	13	
	Age group	5-12 y/o	1-4 y/o	
	Serum phosphorus (mg/dL)			
	Baseline, mean	2.38	2.51 [‡]	
	Week 40, mean	3.30	3.47 [‡]	
	RSS total score			
	Week 40, LS mean change from baseline	-55% [‡]	-59%	
	Week 64, LS mean change from baseline	-52% [‡]		
	RGI-C global score			
	Week 40, LS mean	+1.66	+2.33	
	Week 64, LS mean	+1.56		
	Height Z-score (SD)			
	Week 40, mean change from baseline	+0.19	-0.20	
	Serum alkaline phosphatase			
	Week 40, mean change from baseline	-15%	-36%	
	<p>*efficacy data shown are for the 26 patients in study CL201 who received injections every 2 weeks (the remaining 26 patients received injections every 4 weeks)</p> <p>‡primary efficacy endpoint; p<0.0001 for change from baseline</p>			
<ul style="list-style-type: none"> ○ Increases in serum phosphorus were consistent among nearly all patients ○ There were also improvements shown in renal phosphate wasting (TmP/GFR) and in serum 1,25(OH)₂vitamin D levels ○ Rickets scores improved more in patients with higher baseline RSS, and showed little change in patients with lower baseline RSS 				

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> ○ Rickets scores improved more in girls than in boys; the number of non-white patients was insufficient for evaluation ○ In study CL201, Week 88 data were available for the first 36 patients enrolled; serum phosphorus, rickets scores and height Z-scores were stable, similar to week 64 ○ Lack of control groups is a limitation of these studies; historical data on 30 children age 5-14 y/o with XLH receiving conventional therapy showed smaller improvements in rickets scores <p><u>Adult XLH</u></p> <ul style="list-style-type: none"> ● Efficacy was established in a randomized, double-blind, placebo controlled phase 3 study (CL303), supplemented by bone biopsy data from a smaller phase 3 study (CL304) ● Enrollment criteria: patients age 18-65 y/o with XLH, hypophosphatemia and substantial skeletal pain (BPI-Question 3 = worst pain in previous 24 hrs, score of ≥4 on 0-10 scale) <p>Study CL303:</p> <ul style="list-style-type: none"> ● 134 patients were randomized to burosumab (N=68) or placebo (N=66) injections; mean age 40 y/o; 65% female; 81% white, 16% Asian, 91% non-Hispanic ● Efficacy endpoints in adults (study CL303): <ul style="list-style-type: none"> ○ Serum phosphorus: Mean value at midpoints of 4-week dosing intervals from baseline to week 24 within normal range (primary endpoint) ○ Skeletal pain: BPI-Q3, change from baseline to week 24 ○ WOMAC (Western Ontario and McMaster University Arthritis Index): Stiffness and Physical Function domain scores; instrument designed for use in osteoarthritis, considered not suitable for this XLH program by FDA ○ Secondary PD endpoints: TmP/GFR, serum 1,25(OH)₂vitamin D level 	<p><u>Adult XLH</u></p> <p>Serum phosphorus normalized in most adult XLH patients, however, pain scores showed little change, most likely because the origins of pain in this population are complex and multifactorial. In addition, a longer duration of treatment may be necessary for a more complete assessment of the effect of burosumab on pain and functional outcomes. There was evidence of substantial reduction in osteomalacia, as shown by bone biopsy findings and enhanced healing of radiographic pseudofractures and fractures. This indicates an improvement in bone health which would likely benefit many adults with XLH, especially those with</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons																																	
	<ul style="list-style-type: none"> ○ Healing of osteomalacia-related pseudofractures and fractures that were identified by skeletal survey at baseline ● Results: Most patients in the burosumab group reached and maintained normal serum phosphorus throughout the dosing cycles; improving trends in pain scores with burosumab did not reach clinical or statistical significance compared to placebo; healing of osteomalacia-related bone lesions appears to be improved with burosumab <table border="1" data-bbox="373 613 1434 1209"> <thead> <tr> <th data-bbox="373 613 1037 695">Study CL303 endpoint</th> <th data-bbox="1037 613 1224 695">Placebo N=66</th> <th data-bbox="1224 613 1434 695">Burosumab N=68</th> </tr> </thead> <tbody> <tr> <td data-bbox="373 695 1037 776">Patients with normal serum phosphorus at midpoint of dose intervals*</td> <td data-bbox="1037 695 1224 776">5/66 (8%)</td> <td data-bbox="1224 695 1434 776">64/68 (94%)</td> </tr> <tr> <td data-bbox="373 776 1037 816">Serum phosphorus (mg/dL)</td> <td data-bbox="1037 776 1224 816"></td> <td data-bbox="1224 776 1434 816"></td> </tr> <tr> <td data-bbox="373 816 1037 857">Baseline, mean</td> <td data-bbox="1037 816 1224 857">1.92</td> <td data-bbox="1224 816 1434 857">2.03</td> </tr> <tr> <td data-bbox="373 857 1037 898">Midpoint of dose intervals to week 24, mean</td> <td data-bbox="1037 857 1224 898">2.08</td> <td data-bbox="1224 857 1434 898">3.24</td> </tr> <tr> <td data-bbox="373 898 1037 938">End of dose intervals to week 24, mean</td> <td data-bbox="1037 898 1224 938">2.05</td> <td data-bbox="1224 898 1434 938">2.72</td> </tr> <tr> <td data-bbox="373 938 1037 979">BPI-Q3 score (worst pain)</td> <td data-bbox="1037 938 1224 979"></td> <td data-bbox="1224 938 1434 979"></td> </tr> <tr> <td data-bbox="373 979 1037 1019">Baseline, mean</td> <td data-bbox="1037 979 1224 1019">6.54</td> <td data-bbox="1224 979 1434 1019">6.81</td> </tr> <tr> <td data-bbox="373 1019 1037 1060">Week 24, mean[‡]</td> <td data-bbox="1037 1019 1224 1060">6.09</td> <td data-bbox="1224 1019 1434 1060">5.82</td> </tr> <tr> <td data-bbox="373 1060 1037 1141">Pseudofractures or fractures at baseline: proportion healed at week 24</td> <td data-bbox="1037 1060 1224 1141">7/91 (8%)</td> <td data-bbox="1224 1060 1434 1141">28/65 (43%)</td> </tr> <tr> <td colspan="3" data-bbox="373 1141 1434 1209"> *primary endpoint; p<0.0001 for burosumab-placebo difference ‡p-value = 0.09 for treatment group difference in change from baseline </td> </tr> </tbody> </table> <ul style="list-style-type: none"> ● TmP/GFR and serum 1,25(OH)₂vitamin D also increased with burosumab ● Efficacy for the primary endpoint was consistent across subgroups (age, gender, race) ● Serum phosphorus in the burosumab treatment group was stable through week 48 	Study CL303 endpoint	Placebo N=66	Burosumab N=68	Patients with normal serum phosphorus at midpoint of dose intervals*	5/66 (8%)	64/68 (94%)	Serum phosphorus (mg/dL)			Baseline, mean	1.92	2.03	Midpoint of dose intervals to week 24, mean	2.08	3.24	End of dose intervals to week 24, mean	2.05	2.72	BPI-Q3 score (worst pain)			Baseline, mean	6.54	6.81	Week 24, mean [‡]	6.09	5.82	Pseudofractures or fractures at baseline: proportion healed at week 24	7/91 (8%)	28/65 (43%)	*primary endpoint; p<0.0001 for burosumab-placebo difference ‡p-value = 0.09 for treatment group difference in change from baseline			<p>more severe disease, or improve bone healing in patients with active fractures or undergoing bone surgery.</p>
Study CL303 endpoint	Placebo N=66	Burosumab N=68																																	
Patients with normal serum phosphorus at midpoint of dose intervals*	5/66 (8%)	64/68 (94%)																																	
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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Study CL304:</p> <ul style="list-style-type: none"> • 14 adults with XLH, treated with open label burosumab • Objective: Evaluate effect on osteomalacia by bone histomorphometry • Double labeled bone biopsies obtained at baseline, week 48 • 11 patients with evaluable biopsies; all showed osteomalacia (excess osteoid) at baseline and improvement at week 48: <ul style="list-style-type: none"> • Osteoid volume (OV/BV): Mean decline 57% from baseline (primary endpoint) • Osteoid thickness (O.Th): Mean decline 33% • Mineralization lag time (MLt): Mean decline 74% <p><u>Other benefits of burosumab</u> (in addition to efficacy in XLH) as compared to conventional therapies</p> <ul style="list-style-type: none"> • Less frequent administration/ improved convenience vs. conventional therapy • Possible improved compliance • Fewer blood draws and urine collections • Likely improved safety (e.g. nephrocalcinosis, hyperparathyroidism) 	
<p>Risk and Risk Management</p>	<ul style="list-style-type: none"> ▪ Safety database: 65 children (age 1-12 years) and 175 adults (≥18 years) received burosumab in repeat-dose studies, almost all for ≥6 months ▪ Safety concerns: <ul style="list-style-type: none"> ○ Hyperphosphatemia (risk factor for nephrocalcinosis) <ul style="list-style-type: none"> ▪ Pediatric: 3/65 patients had dose reduction for high-normal serum phosphorus levels ▪ Adult: 17/134 patients in study CL303 had at least one phosphorus level above normal (>4.5 mg/dL), and 8 required dose reduction 	<p>Burosumab appears to be generally safe and well tolerated. It should not be used concomitantly with oral phosphate or active vitamin D analogs (e.g. calcitriol) or in patients with normal serum phosphorus at baseline. It is important for serum phosphorus to be monitored for at least 3 months after starting treatment. These issues can be adequately addressed</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> ○ Nephrocalcinosis (abnormal mineralization in kidneys): In studies CL201 and CL303, more patients had small increases (worsening) in nephrocalcinosis scores than small decreases, but no large increases and no difference from placebo ○ Ectopic mineralization in the heart: No significant abnormalities to date seen on scheduled echocardiograms ○ Renal function: Potential for impairment due to mineralization or due to antibody-dependent cellular cytotoxicity (based on in vitro assay findings); no evidence of renal function impairment to date ○ Hyperparathyroidism: 3 possible cases in clinical studies were probably caused by prior phosphate therapy; no evidence of increase in serum PTH caused by burosumab ○ Spinal stenosis: High prevalence in adults with XLH; 6/176 patients in adult studies underwent surgery during the study ○ Injection site reactions: 58% of children, 12% of adults (same as placebo); almost invariably mild ○ Hypersensitivity reactions such as rash, urticaria; not severe or life-threatening, except for an instance of angioedema that was probably related to concomitant treatment with lisinopril ○ Restless legs syndrome: 9% of adult patients 	<p>through product labeling and there is no indication for a REMS.</p> <p>There are uncertainties about the potential for nephrocalcinosis and/or renal impairment with long term use, and about safety during pregnancy or lactation. These should be addressed in a postmarketing study.</p>

1.4. Patient Experience Data

Patient experience data pertaining and submitted with this application are outlined in Table 1.

Table 1: Patient Experience Data Relevant to this Application

x	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
x	Clinical outcome assessment (COA) data, such as	
	x Patient reported outcome (PRO)	Studies CL201, CL303
	□ Observer reported outcome (ObsRO)	
x	Clinician reported outcome (ClinRO)	Studies CL201, CL303
	□ Performance outcome (PerfO)	
□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	Patient-focused drug development or other stakeholder meeting summary reports	
x	Observational survey studies designed to capture patient experience data	Study CL001
x	Natural history studies	Study CL002
□	Patient preference studies (e.g., submitted studies or scientific publications)	
□	Other: (Please specify)	
x	Patient experience data that were not submitted in the application, but were considered in this review:	
□	Input informed from participation in meetings with patient stakeholders	
x	Patient-focused drug development or other stakeholder meeting summary reports	A meeting with patients and the XLH network was held 12/4/2017
□	Observational survey studies designed to capture patient experience data	
□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

X-linked hypophosphatemia (XLH) is caused by inactivating mutations in the *PHEX* gene (phosphate-regulating gene with homology to endopeptidases on the X chromosome). The *PHEX* loss of function causes osteocytes to secrete excess fibroblast growth factor-23 (FGF23), which is a key physiologic regulator of phosphate and vitamin D metabolism. FGF23 binds to the FGFR1c receptor and α -klotho co-receptor on proximal renal tubule cells, causing two effects: (1) reduced expression of sodium-phosphate co-transporters (NaPi-IIa and NaPi-IIc), causing urinary phosphate wasting; and (2) downregulation of 1α -hydroxylase with reduced secretion of 1,25 dihydroxyvitamin D, causing reduced calcium and phosphate absorption in the gut. In XLH, excess FGF23 leads to hypophosphatemia, resulting in inadequate skeletal mineralization, i.e. rickets and osteomalacia. It is unknown whether excess FGF23 may also have direct effects on bone mineralization (independent of phosphate), or whether *PHEX* loss of function may impair mineralization through other mechanisms (independent of FGF23).

XLH affects approximately 1/20,000 live births, with an estimated prevalence of 3,000 pediatric and 12,000 adult patients in the U.S., and is one of the most common metabolic bone diseases in children. XLH was originally known as familial vitamin D resistant rickets. The differential diagnosis includes nutritional rickets (deficiency of vitamin D and/or calcium) and a variety of other disorders involving vitamin D absorption or metabolism, and other disorders of renal phosphate wasting. Laboratory findings in untreated patients with XLH typically include normal serum calcium and 25-OH-vitamin D, normal or slightly elevated PTH, low serum phosphorus, low renal tubular reabsorption of phosphate (TRP) and tubular maximal reabsorption of phosphate per glomerular filtration rate (TmP-GFR), low-normal (i.e. inappropriately low for hypophosphatemia) serum 1,25(OH)D, and elevated serum FGF23. In children, serum alkaline phosphatase is usually elevated, and is believed to correlate with severity of rickets.

Most patients with XLH are diagnosed in early childhood with leg bowing after beginning to walk, or because of a family history. The characteristic radiographic changes of rickets are readily identified in the metaphyses of rapidly growing bones such as the distal femur, proximal tibia, distal radius and ulna and proximal humerus. Because of the abnormal growth plates (rickets) and deficient mineralization of bone tissue generally (osteomalacia), most children with XLH have impaired growth and progressive bowing of femur and tibia with genu varum (outward bowing of the lower legs). Other common deformities are rotational torsion of the tibia with intoeing, and genu varum (knock-knees). Most children experience gait abnormalities, lower extremity pain and short stature, which is mostly related to shortness of the legs, rather than the trunk. Surgery to correct bowing, including femoral and/or tibial osteotomy and fixation with plates or medullary rods, is required in some cases and is usually postponed until growth plates have closed.

Many (but not all) adults with XLH experience continued or recurrent symptoms of bone or joint pain, stiffness or functional limitations, mainly involving the lower extremities. In many

cases, such symptoms are related to persistent malalignment of bones and joints, leading to early development of osteoarthritis, especially at the knee. In addition, the defect in mineral metabolism persists; essentially all adults with XLH continue to have hypophosphatemia and histomorphometric evidence of moderate to severe osteomalacia. More severe osteomalacia appears to correlate with presence and severity of bone pain. Osteomalacia may lead to insufficiency fractures of the femur or tibia, or to pseudofractures. The latter are identified as Looser zones on radiographs and represent areas of cortical lucency due to poorly mineralized new bone at areas of stress, typically along the medial border of the proximal femur. In some cases, bowing deformities may worsen in adulthood.

Enthesopathy (calcification of ligaments and tendons and development of osteophytes) is a somewhat paradoxical but common feature of XLH that develops in adulthood, especially after age 40. This condition has been reported in individuals with minimal prior exposure to treatment with phosphate or calcitriol, and is believed to be a primary manifestation of XLH, although the mechanism is unknown. Enthesopathy may be associated with significant pain and/or limitations in range of motion. Calcification of spinal ligaments may result in spinal stenosis in a substantial number of patients.

Dental abscesses are common in children and adults with XLH, apparently related to poorly mineralized dentin. XLH patients may also experience fatigue or muscle weakness, which may be related to hypophosphatemia.

2.2. Analysis of Current Treatment Options

Treatment of pediatric XLH

There are no approved therapies for XLH. Most children with the disease are treated, from the time of diagnosis until growth stops, with oral supplements of phosphate and activated vitamin D analogs (usually calcitriol). Oral phosphate must be taken in 3-5 divided doses per day because of rapid renal excretion, and may cause dose-related GI adverse effects. Calcitriol augments the increase in serum phosphorus, which allows somewhat lower doses of phosphate, and helps to limit the hyperparathyroidism that tends to occur when phosphate is given alone. Therefore, most patients receive both phosphate and calcitriol; the combination is referred to here as conventional therapy.

Conventional therapy for XLH is not standardized, and reported doses have varied over a wide range. The following table lists the pediatric starting doses used by two leading referral centers, one in the US and one in Europe. As noted, the latter generally uses higher phosphate doses. Calcitriol is the vitamin D analog most widely used in the US for XLH; European centers use calcitriol or alfacalcidol, but the latter is not available in the US. Compared to these 1 α -hydroxylated (activated) analogs, vitamin D itself is rarely used for XLH because of lower efficacy and possibly greater toxicity.

Table 2: Conventional therapy for treatment of pediatric XLH (not approved for XLH‡)

	Formulations	Dosing recommendations	Important safety and tolerability issues
Phosphate	Sodium and/or potassium phosphate (e.g. Neutraphos, K-Phos, Phospho-soda) Oral solution; powder or tablets for oral solution	Daily dose of elemental phosphorus: US*: 20-40 mg/kg Europe**: 45-60 mg/kg 3-5 divided doses	Abdominal pain, diarrhea Hyperparathyroidism Nephrocalcinosis
Active vitamin D	Calcitriol (1,25-OH-D ₃) (Rocaltrol)‡ Oral solution, capsules	US*:20-30 ng/kg/day Europe**: 0.5-1.0 mcg/day 2-3 divided doses	Hypercalcemia Hypercalciuria Nephrocalcinosis Nephrolithiasis
	Alternative 1 α -hydroxylated vitamin D analogs: Alfacalcidol (1 α -OH-D ₃) 1-2 mcg/day‡‡ Doxercalciferol (Hectoral) Paricalcitol (Zemplar)		
*Carpenter et al, <i>JBMR</i> (2011), 26:1381-1388 **Linglart et al, <i>Endocr Connect</i> (2014), 3: R13-R30; doses recommended for prepubertal children ‡Calcitriol is approved in the US for management of secondary hyperparathyroidism and metabolic bone disease in patients with renal failure, hypocalcemia and metabolic bone disease in dialysis patients, and hypocalcemia in patients with hypoparathyroidism ‡‡Alfacalcidol, which is converted to calcitriol by 25-hydroxylation in the liver, is widely used to treat XLH in Europe, Canada and Japan, but is not available in U.S.			

The major safety concerns with conventional therapy are hyperparathyroidism, which may require parathyroidectomy, and nephrocalcinosis/nephrolithiasis. The latter result from the increase in urinary phosphate, and potentially also from increased urinary calcium (from calcitriol). Aggressive treatment aimed at normalizing fasting serum phosphorus appears to increase the risk of hyperparathyroidism or nephrocalcinosis. Thus, it is generally agreed that with conventional therapy, serum phosphorus should remain below normal range.

Patients require careful lab monitoring, typically at 3-month intervals, including serum calcium, phosphorus, creatinine and PTH, and urine calcium and urine creatinine. Dose reductions may be required for hypercalcemia or hypercalciuria (i.e. reduced dose of calcitriol), or elevated PTH (reduced dose of phosphate and/or increased dose of calcitriol). Periodic renal ultrasound to screen for nephrocalcinosis is recommended by the above-referenced US and European groups at 2-5 year or 1-2 year intervals, respectively. Worsening of nephrocalcinosis is considered to warrant decreased dosages, but progression to renal failure is rare.

Efficacy response in children with XLH may be monitored by assessments of radiographic rickets (usually the knees and/or wrists) and of serum alkaline phosphatase, which generally improve over a period of months; and clinical features including growth, deformities, bone pain and physical function. If response is suboptimal despite adequate compliance, doses of phosphate

and/or calcitriol may be increased as tolerated based on the safety lab parameters discussed above. Because monitoring and dose adjustments to balance efficacy and safety may be complex, many XLH patients are treated at a small number of tertiary referral centers.

Although bone biopsies are rarely used to monitor treatment, biopsy studies of children treated with conventional therapy have shown improvements in mineralization of the growth plate, and reduction in osteoid thickness and volume.

Regarding the key long-term goals of improving growth deficits and leg deformities in children with XLH, the benefits of conventional therapy are difficult to quantify, due to a lack of controlled studies. Despite reports of short-term improvements in radiographic rickets and in growth velocity after starting treatment, a longitudinal study of 62 children treated throughout childhood and adolescence showed little change over time in average height Z-score within the range of about -1.5 to -2.0; mean final height was 5'3" for boys and 5'0" for girls. (Linglart 2014)

Similarly, conventional therapy generally improves, but usually does not completely correct leg bowing and other deformities. Linglart (2014) reported that the use of osteotomy or other corrective surgery declined from 89% to 11% of patients after the development of current therapy in the 1970s. Earlier age at initiation of therapy improves the prognosis for resolving deformities and for long-term growth.

Treatment with phosphate/calcitriol is associated with further increases in serum FGF23, in both children and adults with XLH, demonstrating that the feedback loop with serum phosphorus remains intact in these patients. The clinical significance of this effect with respect to efficacy or safety, if any, is unknown.

Growth hormone is sometimes used as adjunctive therapy in children with XLH and severe short stature, but adequately controlled trials to show improved adult height have not been conducted, and adverse effects including worsening leg deformities have been reported.

Treatment of Adult XLH

After growth plates have closed, the goals of treatment are less clear, and many adults with XLH stop therapy. Given a lack of controlled studies to show benefit and the continued risk of long-term safety issues (hyperparathyroidism, nephrocalcinosis), there is no consensus that asymptomatic adults require continued therapy. Carpenter (2011) considers the following adult patient categories to be appropriate for continued therapy:

- Spontaneous insufficiency fractures, usually of the femur, tibia or metatarsals, which are believed to heal better with medical therapy
- Pending orthopedic procedures e.g. joint replacement, where healing is also believed to be enhanced with concurrent therapy
- Elevated serum alkaline phosphatase, considered to usually represent extensive osteomalacia

- Disabling skeletal pain in lower extremities

Perhaps the most objective evidence of treatment benefit in adults with XLH was shown prospectively in an open-label study: 6 symptomatic adults with pre-treatment bone biopsies showing severe osteomalacia demonstrated improvements with phosphate/calcitriol therapy, osteoid volume (OV/BV) declined by 5-93% from baseline (mean 50%), and osteoid thickness declined by 25-60% (mean 47%). However, these parameters remained well above reference ranges in all but one of the 6 patients. Pain scores also improved in 14/16 (87.5%) patients treated in this study, however there was no control group. (Sullivan et al, *JCEM* 1992; 75:879)

It is not known whether conventional therapy has an effect on enthesopathy or spinous ligament calcification in XLH, either improving or exacerbating these conditions. It is also uncertain whether phosphate/calcitriol has any effect on prevention of dental abscesses.

When treatment is indicated in an adult, dosing requirements are generally lower (on a per kg basis) than in children; normal range of serum phosphorus is also lower in adults, which may in part reflect reduced skeletal needs after epiphyseal closure. For adults, Carpenter recommends starting doses of 750-1000 mg phosphate (still in 3-4 divided doses) and 0.5-0.75 mcg calcitriol daily. Frequent laboratory monitoring and dose adjustments are required, as in children.

Cinacalcet, a calcium-sensing receptor modulator that suppresses PTH levels, is sometimes used (off-label) in adults with XLH and refractory hyperparathyroidism, as an alternative to surgery. Cinacalcet is not recommended for pediatric patients based on safety concerns of fatal outcomes as a result of hypocalcemia.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Burosumab is an original new biologic product that has never been marketed in the U.S.

The main focus of development to date has been for the treatment of XLH under IND 076488. The applicant is also investigating burosumab in the treatment of tumor-induced osteomalacia

(b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

Burosumab, originally known as KRN23, was initially developed by Kyowa Hakko Kirin Pharma (KKP).

A Pre-IND meeting (7/23/2007) involved discussion of nonclinical data needed to support a first in human study, especially pertaining to the potential for ectopic mineralization related to KRN23 pharmacology. Regarding plans for clinical studies, it was agreed that children with XLH may derive the greatest benefit from treatment, but that adults should first be evaluated for safety and efficacy. The Division stated that in addition to serum phosphorus and other biochemical markers, clinical endpoints related to bone health would be required to establish efficacy.

The initial IND 076488 submission (4/29/2008) included nonclinical studies and a first in human single dose study protocol (KRN23-US-02). Upon review, concerns remained about soft tissue mineralization and hyperphosphatemic deaths in animal studies, and about the proposed dosing and enrollment of healthy volunteers who, with normal serum phosphorus and FGF23 levels, may be more susceptible to mineralization toxicity than XLH patients. Thus, a full clinical hold was imposed on 6/4/2008. Subsequently, the protocol was revised to specify enrollment of adults with XLH, limit higher doses and include additional safety monitoring; the clinical hold was removed on 10/3/2008.

On 12/14/2009, Orphan Drug designation was granted for the treatment of XLH.

Based on the clinical phase 1 and nonclinical data, KKP submitted a repeat-dose protocol (KRN23-INT-001) in adults with XLH on 12/29/2010. Subjects were planned to receive 4 successive SC doses of burosumab (0.05, 0.1, 0.3 and 0.6 mg/kg) at 28-day intervals. A planned extension KRN23-INT-002 (12 monthly doses, with maximal dose 1.0 mg/kg) was later added. Dosing in these phase 2 studies (total enrollment = 29) was titrated by serum phosphorus levels as a means of dose-finding. The Division advised that a randomized, placebo-controlled study would be preferred, however, the sponsor stated that inclusion of a control group would raise ethical and enrollment issues (letter to sponsor 6/13/2011 and teleconference 10/13/2011). Subsequently (2/23/2012), the sponsor amended these protocols to add a placebo-controlled substudy which would include bone biopsies. On 8/7/2013, the sponsor notified the Division that enrollment in the studies was ended due to slow accrual, and the bone substudy was terminated with only 2 subjects enrolled and no biopsies performed. The Division acknowledged this and stated that the sponsor should “address the Division’s concern regarding the lack of placebo-controlled data” and “address the lack of bone-specific endpoints....in your development plan” (letter 11/12/2013).

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On 10/15/2013, FDA was notified that the transfer of IND 076488 sponsorship from KKP to Ultragenyx Pharmaceuticals was complete. The Orphan Drug designation was transferred on 5/23/2014.

On 5/28/2014, a Type C meeting was held in order to discuss pediatric development plans, including a proposed 64-week open-label phase 2 study in children with XLH and rickets age 5-12 years old, with comparison of Q2W and Q4W dosing and dose titration by serum phosphorus. The study did not include a control group; it was agreed that a placebo arm would be ethically unacceptable, given that conventional therapy (phosphate/calcitriol) has demonstrated positive effects on growth and deformities. The Division recommended an active control arm with phosphate/calcitriol, noting the advantages of a concurrent control over retrospective historical data. The applicant observed the challenges with conventional therapy e.g. lack of standardization; there was no agreement on this issue (a control group was ultimately not included in the study). There was agreement on the enrollment criteria, the main pharmacodynamic (PD) and efficacy endpoints, i.e., serum phosphorus, radiographic indices of rickets and bowing, and growth parameters, and safety monitoring.

This pediatric study (UX023-CL201) began enrollment on 7/2/2014 with an initial goal of ~30 children; protocol amendment 3 (submitted 3/13/2015) expanded enrollment to ~50 children. Based on preliminary PD and radiographic data showing that response was generally more favorable in children with greater severity of rickets and with Q2W compared to Q4W dosing, the protocol was amended to require baseline RSS (Rickets Severity Score) ≥ 1.5 for the "expansion cohort" (amendment 3) and, for the study extension beyond week 64, to transition Q4W patients to Q2W (amendment 5).

On 2/26/2015, a Type C Guidance meeting was held to discuss a planned phase 3 study of adults with XLH. Agreement was reached on the general study design (randomized, double blind, placebo-controlled, 48-week duration with primary analysis at 24 weeks); enrollment criteria (adults with symptomatic XLH); and planned dose (1.0 mg/kg Q4W). In regard to the applicant's plan to use peak serum phosphorus as the primary endpoint, the Division stated that serum phosphorus alone would not be sufficient, and proposed addition of a co-primary endpoint such as osteomalacia-related pain or direct evaluation of osteomalacia by bone biopsy. The applicant proposed to use the WOMAC for patient-reported outcomes of pain, stiffness and physical function. Clinical Outcome Assessments (COA) consultants expressed concerns regarding the use of WOMAC, an instrument developed to assess osteoarthritis of the knee or hip, in patients with XLH, and recommended consideration of the BPI-Question 3 (worst pain within 24 hrs) and re-evaluation of other Patient-Reported Outcomes (PROs). No agreement was reached on the PRO endpoints. In regard to osteomalacia, the applicant indicated their plan to conduct bone biopsies in a smaller, separate phase 3 study. On 8/6/2015, protocols were submitted for two adult XLH phase 3 studies: CL303, a randomized, placebo controlled study in ~120 adults, with serum phosphorus as primary endpoint and BPI-

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Q3 as secondary efficacy endpoint; and CL304, an open label bone biopsy study in ~10 adults with osteomalacia parameters as primary endpoint.

Fast Track designation was granted on 6/30/2015 for treatment of XLH.

An End of Phase 2 meeting was held on 12/10/2015. Based on the initial phase 2 data in 5-12 years old patients (study CL201), the applicant indicated plans for two additional pediatric studies: a single arm, open-label phase 2 study in 1-4 years old patients (CL205) and a phase 3 study in 1-12 years old patients (CL301), which would compare burosumab with active-control phosphate/ calcitriol. Both of these studies use Q2W dosing. (b) (4)

The CL205 and CL301 protocols were submitted on 4/4/2016; (b) (4)

. Studies CL205 and CL301 are currently ongoing and fully enrolled, although no CL301 data are yet available.

Breakthrough Therapy designation was granted on 6/22/2016, for the treatment of XLH in pediatric patients one year of age and older. At the recommendation of DBRUP, treatment of adults with XLH was not included in the request for this designation.

On 11/10/2016, a Type B Initial Comprehensive Multidisciplinary Breakthrough meeting was held. The timing of BLA submission was discussed; DBRUP recommended delay until mid-2017, when week 64 data from study CL201 (pediatric) and week 24 data from study CL303 (adult) would become available. The CL303 data were expected to be particularly valuable because of the lack of controls in all other burosumab studies. The applicant outlined plans to use a historical control study (CL002) to complement the CL201 pediatric data; DBRUP indicated that the acceptability of these data and analyses would be a BLA review issue. (b) (4)

On 5/15/2017, a waiver for carcinogenicity studies was granted.

On 6/19/2017, a Pre-BLA meeting was held. The applicant indicated plans to use propensity score analyses to compare the effect on rickets of burosumab (study CL201, 64 week data) versus conventional therapy (study CL002), and to also submit 24-week data from study CL205. Regarding the adult study CL303, the statistical plan (submitted 2/10/2017) had established 3 secondary PRO endpoints (BPI-Q3 per the original protocol, plus the WOMAC Physical Function

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and Stiffness scores). DBRUP indicated that suitability of these PRO endpoints, particularly the WOMAC, for labeling would require in-depth review. DBRUP also requested inclusion of any available bone biopsy data from study CL304, given the importance of osteomalacia endpoints in the evaluation of efficacy. The applicant acknowledged the need to provide further rationale for their proposed dosing regimens.

Also briefly discussed at the 11/10/2016 and 6/19/2017 meetings was the applicant's plan for a postmarketing Disease Monitoring Program (XLH-DMP) to gather additional long-term pediatric and adult safety and efficacy data. This patient registry, also designated as study UX023-CL401, would follow burosumab-treated patients for up to 10 years and was planned to launch in late 2017 or early 2018 (see section 14 of this review).

On 7/11/2017, rare pediatric disease designation was granted by the Office of Orphan Products Development.

The BLA submission also includes a request for Rare Pediatric Disease Priority Review Voucher.

3.3. Foreign Regulatory Actions and Marketing History

In December 2017, the European Medicines Agency Committee for Medicinal Products for Human Use recommended granting conditional marketing authorization for the treatment of XLH with radiographic bone disease in children age ≥ 1 year of age and adolescents with growing skeletons. (b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations was consulted for this BLA. Four clinical sites participating in pediatric study UX023-CL201 and/or adult study UX023-CL303 were inspected. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Site 139, Anthony Potale, MD, UCSF Medical Center, was selected due to large enrollment in both study 201 and study 303. A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection with an observation of protocol violations. For Protocol UX023-CL201, five of the 8 enrolled pediatric subjects received an X-ray of the standing long leg at

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Week 40, which was not required by the protocol. This protocol violation was reported to FDA and the IRB. For Protocol UX023-CL303, the AE of mild general bone pain for Subject (b) (6) (in the placebo group) was not reported. The bone pain resolved after the treatment of three doses of ibuprofen 200 mg. There was no evidence of under-reporting of other adverse events. Dr. Portale adequately responded to the inspection findings in a letter dated December 28, 2017. Additionally, the source data necessary to verify the primary efficacy endpoint were not available at the site during the inspection. However, OSI later obtained source electronic data from the vendor (through the sponsor) and was able to verify the RSS and RGI-C scores for Study UX023-CL201 and the serum phosphorus levels for Study UX023- CL303. This site was classified as Deviation(s) from regulations (VAI).

Site 156, Eric Imel, MD, Indiana University, was selected due to large enrollment in both study 201 and study 303. This site was classified as no deviation from regulation (NAI).

Site 141, Agnes Linglart, MD, Hospital Bicetre, France enrolled patients for pediatric study 201 and was selected to ensure consistency of treatment between US and foreign clinical sites. This site was classified as NAI.

Site 186, Peter Kamenicky, MD, CHU de Bicetre, France enrolled patients for adult study 303 and was selected for large enrollment and to ensure consistency of treatment between US and foreign clinical sites. This site was classified as NAI.

4.2. Product Quality

The review team from the Office of Biotechnology Products recommends approval of Crysvita (burosumab). Burosumab is a human IgG1 (K) monoclonal antibody that binds to fibroblast growth factor 23 (FGF 23) to inhibit the interactions between FGF23 and the Klotho-FGF receptor complex. Burosumab consists of 4 polypeptide chains (2 identical heavy chains, 446/447 amino acids each, and 2 identical light chains, 213 amino acids each) and has a molecular weight of 147 kDa.

Drug Substance and Drug Product manufacturing occur in the same facility.

Drug Substance

Burosumab is produced from a recombinant DNA-derived Chinese Hamster Ovary (CHO) cell line using standard cell culture techniques. The master cell bank (MCB) and working cell bank (WCB) have been adequately characterized and tested. The drug substance manufacturing begins (b) (4)

(b) (4)

Tables 1 and 2, pages 4 – 6 of the Office of Biologic Products ATL memo outline the critical quality attributes of the burosumab drug substance. The data provided in the BLA supports a shelf life of (b) (4) months for the burosumab drug substance when stored at - (b) (4) °C.

Drug Product

The drug product manufacturing process steps include (b) (4)

All accepted vials are shipped to a labeling and packaging facility for labeling with approved labels before storage at 2-8°C. The container closure system for burosumab drug product consists of a 5 mL vial, a rubber stopper, and an aluminum sealing cap with a (b) (4) top. Appropriate compatibility studies were performed for the container closure system. Table 1, pages 4, 5 and Tables 3, pages 7, 8 of the Office of Biologic Products ATL memo outline the critical quality attributes of the burosumab drug product.

The drug product is supplied in single use vials of 10 mg/mL, 20 mg/mL, or 30 mg/mL strength. Each vial has a 5mL capacity with a labeled volume of 1 mL. As outlined in the table below, the drug product formulation consists of L-histidine (10 mmol/L), D-sorbitol (252 mmol/L), Polysorbate 80 (0.5 mg/mL), L-methionine (10 mmol/L), Hydrochloric acid, (b) (4)% (as needed), and Water for Injection at pH 6.25. The extractable volume is 1.0 mL. The dating period for burosumab drug product is 36 months at 2-8°C, protected from light.

Table 3 Burosumab Drug Product Composition

Component	Function	Concentration	Quantity per Vial		
			10 mg/mL	20 mg/mL	30 mg/mL
Burosumab	API	10, 20, or 30 mg/mL	10 mg	20 mg	30 mg
L-histidine	(b) (4)	10 mmol/L	1.552 mg	1.552 mg	1.552 mg
D-sorbitol		252 mmol/L	45.91 mg	45.91 mg	45.91 mg
Polysorbate 80		0.5 mg/mL	0.500 mg	0.500 mg	0.500 mg
L-methionine		10 mmol/L	1.492 mg	1.492 mg	1.492 mg
Hydrochloride acid (b) (4)%		Adjust to pH 6.25	as required	as required	as required
Water for injection		q.s. to each labeled volume	q.s. to 1.000 mL	q.s. to 1.000 mL	q.s. to 1.000 mL
API – active pharmaceutical ingredient					

q.s.= quantity sufficient
source: Table 3.2.P.1.2.1 page 1, DP and Immunogenicity Review Memo

Microbiology

The drug product quality microbiology parts of this BLA are recommended for approval. Please see Dr. Lakshmi Rani Narasimhan's 1/26/2018 review and 2/9/2018 review amendment for complete details.

Facilities

Kyowa Hakko Kirin Co., Ltd. Takasaki Plant, Takasaki-shi Japan (FEI 3007588904): This site is responsible for master cell bank and working cell bank storage, drug substance manufacturing, drug product manufacturing, quality control for release, and drug product lot release. A Pre-License Inspection was performed 12/11/2017 – 12/21/2017 and a nine item Form FDA 483 was issued. The firm has addressed the items outlined and the facility status is acceptable.

(b) (4) This site is responsible for drug substance (b) (4) testing. The facility status is acceptable.

(b) (4): The site is responsible for drug product vial labeling secondary packaging, and finished drug product lot release. No further evaluation is needed from a facilities prespective.

(b) (4): This site is responsible for drug product vial labeling, secondary packaging and finished drug product lot release. No further evaluation is needed from a facilities prespective.

(b) (4) This site is responsible for drug product vial labeling and secondary packaging. No further evaluation is needed from a facilities prespective.

Environmental Assessment

A claim for a categorical exclusion is being made under 21 CFR 25.31 (a) and (c). This application is for marketing approval of a biologic product comprised of substances that occur naturally in the environment and approval of this application would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. To the applicant's knowledge, no extraordinary circumstances, as described in 21

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CFR 25.21, exist that would result in significant impact to the environment from the discharge of this substance. This waiver request is acceptable.

Labeling

Prescribing information related to Product Quality, and container closure labeling have been reviewed and changes were conveyed to the applicant. The nonproprietary name suffix of twza has been approved by the Agency, therefore, the nonproprietary name for Crysvida will be burosumab-twza.

Postmarketing Commitments

The OBP review team recommends the following postmarketing commitments:

1. Conduct studies to further characterize the burosumab master cell bank (MCB) to support the monoclonality of the MCB.
2. Conduct studies to evaluate effector functions (i.e., antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity) of burosumab. The final PMC report should be submitted based on the outcome of the studies per 21 CFR 601.12.

The applicant concurs with the OBP team that these commitments will be conducted and milestones have been established.

4.3. Devices and Companion Diagnostic Issues

No device or companion diagnostic products are included in this original BLA. Crysvida is to be administered by a healthcare provider and therefore no human factors information was required.

4.4. Consumer Study Reviews

Consumer study reviews are not pertinent to this application.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Burosumab is an IgG1 monoclonal antibody against Fibroblast Growth Factor 23 (FGF23), a member of the FGF19 subfamily of endocrine FGFs. Burosumab increases serum phosphorus and 1,25-dihydroxyvitamin D3 (1,25(OH)₂VitD) levels through inhibition of the suppressive action of FGF23 on (a) renal sodium-phosphate (Na-P) exchange and phosphate reabsorption, and (b) 25-hydroxylation of 1 α (OH)VitD and intestinal phosphate absorption. Burosumab can

counter the FGF23-induced phosphaturia, hypophosphatemia and reduced bone mineralization in patients with X-linked hypophosphatemia (XLH), a heritable phosphate wasting disorder.

The applicant is seeking approval of burosumab for the treatment of X-linked hypophosphatemia (XLH). The recommended initial human dose is 1 mg/kg (adults) or 0.8 mg/kg (children), with a maximum dose of 90 mg, administered by subcutaneous injection every 4 weeks (adults) or every 2 weeks (children).

Burosumab bound with high affinity to rabbit, monkey and human but not rodent FGF23, and inhibited the activity of human, monkey and rabbit FGF23 in cell-based assays. Hence, rabbits and cynomolgus monkeys were used in the in vivo nonclinical studies. The FGFR-binding N-terminal domain of FGF23 appeared to bind to burosumab, and the C-terminal domain to α Klotho. Studies in rabbits and monkeys showed that burosumab increased serum phosphorus and 1,25(OH)₂VitD upon intravenous (IV) and subcutaneous (SC) dosing. Studies in Hyp mice (a murine analogue of XLH) with a murine anti-FGF23 antibody (Ab) showed improvements of hypophosphatemia, longitudinal bone growth, bone mineralization, muscle strength and spontaneous movement.

A reduction in cardiac output was observed in male monkeys after 40 weeks of Q2W dosing with 30 mg/kg IV or SC burosumab (37-47x adult human AUC at 1 mg/kg). The effects were correlated with increases in peak serum phosphorus above 8 mg/dL and associated with mineralization of the heart.

The pharmacokinetic behavior of burosumab was generally similar in rabbits and cynomolgus monkeys, and in male and female animals. C_{max} and AUC increased in dose-related manner. In monkeys, AUC was similar upon IV and SC dosing. AUC was lower in juvenile than adult monkeys at similar IV doses. Some accumulation was observed upon repeat dosing and AUC reached steady state by the 4th dose of 1 mg/kg SC in the monkey.

In rabbits, single dose and 14-week toxicity studies were conducted with Q2W via IV doses of 0, 0.03, 0.3, 3 mg/kg. The main effects included expected increases in serum phosphorus and 1,25(OH)₂VitD at ≥ 0.3 mg/kg and ectopic mineralization in multiple soft tissues e.g. kidney, heart, aorta, lung and parathyroid at 3 mg/kg. Mortality due to mineralization-related cardiac or renal failure was observed at 3 mg/kg in both single and repeat dose studies. Other effects included body weight and RBC decreases, mainly at 3 mg/kg. The NOAEL was 0.3 mg/kg (0.44x adult human AUC) in both single dose and 14-week studies. No anti-drug antibodies (ADA) were detected in rabbits.

In adult monkeys, in 14-week and 40-week studies with burosumab at Q2W with IV or SC doses of 0, 0.03, 0.3, 3, 30 mg/kg, effects included expected increases in serum phosphorus and 1,25(OH)₂VitD at ≥ 0.03 mg/kg and ectopic mineralization in multiple tissues e.g. kidney, heart, aorta, eye, sciatic nerve, muscle, and testis at ≥ 3 mg/kg. Effects were more pronounced in males.

Positive effects on the skeleton were observed at 0.3-3 mg/kg. However, adverse bone effects including reduced bone density, mineralization and strength were observed in males at 30 mg/kg. Other effects included RBC/lymphocyte decreases, serum BUN increase and protein decreases at 3 and/or 30 mg/kg. The NOAEL was 0.3 mg/kg (0.9x adult human AUC) in both 14- and 40-week studies. ADA (anti-drug antibodies) to burosumab were detected in 2 of 36 animals (at 3 mg/kg) in the 14-week study and 1 of 56 animals (at 30 mg/kg) in the 40-week study, respectively.

In juvenile monkeys, in a 40-week study with burosumab at Q2W IV doses of 0, 0.03, 0.3, 3 mg/kg, notable effects included expected increases in serum phosphorus and 1,25(OH)₂VitD at all doses and mineralization in several soft tissues at 0.3 and 3 mg/kg. Positive bone effects were observed at 3 mg/kg. Other effects included RBC decrease at 3 mg/kg. The NOAEL was 0.3 mg/kg (0.3-0.4x pediatric AUC), based on ectopic mineralization. ADA to burosumab were not detected in any animal.

A 14-day study with Q3D SC doses of 0, 3, 10, 30 mg/kg of a murine FGF23-antibody was conducted in wild type (WT) and Hyp mice. The NOAEL was similar in both genotypes (<3 mg/kg), based on increased mineralization in kidney and lung at the LOAEL of 3 mg/kg. However, the incidence and severity of the finding was similar in the 30 mg/kg Hyp mice as in the 3 mg/kg WT mice, which suggests an approx. 10-fold lower sensitivity in Hyp mice.

No genetic toxicology or carcinogenicity studies were conducted with burosumab. The applicant provided a carcinogenicity risk assessment based on a weight-of-evidence approach in the BLA submission. Data from animal and human genetic disease models, in vitro and in vivo cell studies, and the animal toxicity studies with burosumab provided no evidence for a proliferative effect of FGF23 inhibition. The nonclinical review team considered this acceptable.

In an enhanced pre- and post-natal development (ePPND) study in pregnant cynomolgus monkeys with Q2W IV doses during gestation of 0, 0.3, 3, 30 mg/kg IV, there was no teratogenicity and there were no effects on pre- and postnatal development. A small increase in the incidence of combined abortions/embryo-fetal deaths was noted at 30 mg/kg (64x human AUC). An increase in preterm and combined premature and preterm births was observed at 30 mg/kg (64x human AUC), and a small dose-related decrease in the length of the gestation period was observed at 0.3-30 mg/kg (0.9-64x human AUC). However, this was not associated with clear adverse consequences for the infants in the study. The reproductive effects may have been associated with placental mineralization and are probably of low clinical relevance. Burosumab exposure in fetuses and offspring was likely due to transplacental distribution. Data on milk burosumab concentrations were not collected. ADA to burosumab were detected in 2 of 94 maternal animals (at 30 mg/kg) after delivery.

Fertility was not evaluated in specific reprotoxicity studies. Minimal mineralization of rete testis and seminiferous tubules were observed associated with elevated serum phosphorus levels at 3-

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30 mg/kg (11- 47x adult human AUC) in the 40-week monkey study, but semen analysis did not show any changes. Female monkey reproductive organs showed no changes in the repeat dose toxicity studies. Thus, adverse effects on fertility are unlikely.

The main adverse effect of burosumab in the normophosphatemic test animals was ectopic mineralization. In rabbits, monkeys and mice, kidney, lung, aorta, heart and/or connective tissue were most sensitive to mineralization. In all species, mineralization was only observed when peak serum phosphorus level exceeded a threshold of at least 8 mg/dL, and was roughly correlated with peak serum phosphorus above this threshold. Hyp mice were considerably (approx. 10 times) less sensitive to mineralization than WT mice. It is likely that the ectopic mineralization was at least partly caused by the increases in serum phosphorus, but other treatment-related changes, e.g. in serum calcium (Ca) and 1,25(OH)₂VitD, may also have contributed. Other significant toxicities were not observed.

The animal NOAELs were low (0.3-0.9x human AUC exposure) due to the sensitivity of normal animals to mineralization. However, this has limited significance, since, like Hyp mice, XLH patients are expected to be at a reduced risk of ectopic mineralization compared to normal animals or humans. Monitoring for renal and cardiac/aorta calcification was carried out in the clinical program. The risk for ectopic mineralization in XLH patients may be minimized through appropriate monitoring of serum phosphate and calcium.

The positive results observed in an antibody-dependent cellular cytotoxicity (ADCC) assay indicated a potential for immunotoxicity in α Klotho-expressing tissues mediated by α -Klotho binding to the FGF23-burosumab complex. Data from monkey and rabbit studies suggested that significant ADCC-like toxicity was not evident in the kidney, or in parathyroid, choroid plexus or cardiovascular system. However, since this type of hypersensitivity is likely to be species specific, it may be a potential source of risk for humans in α -Klotho expressing tissues.

From a Pharmacology/Toxicology perspective, burosumab can be approved for the treatment of XLH. There are no recommended nonclinical PMCs/PMRs for this BLA.

5.2. Referenced NDAs, BLAs, DMFs

IND 76,488, KRN23 (Sponsor: Kirin Pharma) Reviews Dr. Ron Wange, Dr. Gemma Kuijpers

(b) (4)

NDA 020819 paricalcitol (Zemlar[®]) (Sponsor: Abbott/Abbvie) Review Dr. Dan Coleman

5.3. Pharmacology

Primary pharmacology

FGF23 is produced primarily by osteocytes and belongs to the hormone-like FGF19 subfamily of FGFs with endocrine activity. Its role is to suppress renal phosphate reabsorption in proximal tubules and to decrease 1,25(OH)₂VitD production and increase 1,25(OH)₂VitD catabolism also in the kidney. A role for FGF23 to increase distal tubular calcium (Ca) and Na reabsorption is less well described. Interactions of FGF23 can also occur with other target organs containing FGFR1 or FGFR3 and α-Klotho. These may include parathyroid, heart/aorta (cardiovascular tissues) and brain (choroid plexus). Tissues expressing FGFR alone including thymus, spleen and bone may also be targets of FGF23 (Figure 1 below). Non-specific interactions with tissues containing other FGF receptors while less likely may also occur.

Figure 1 Functions of FGF23

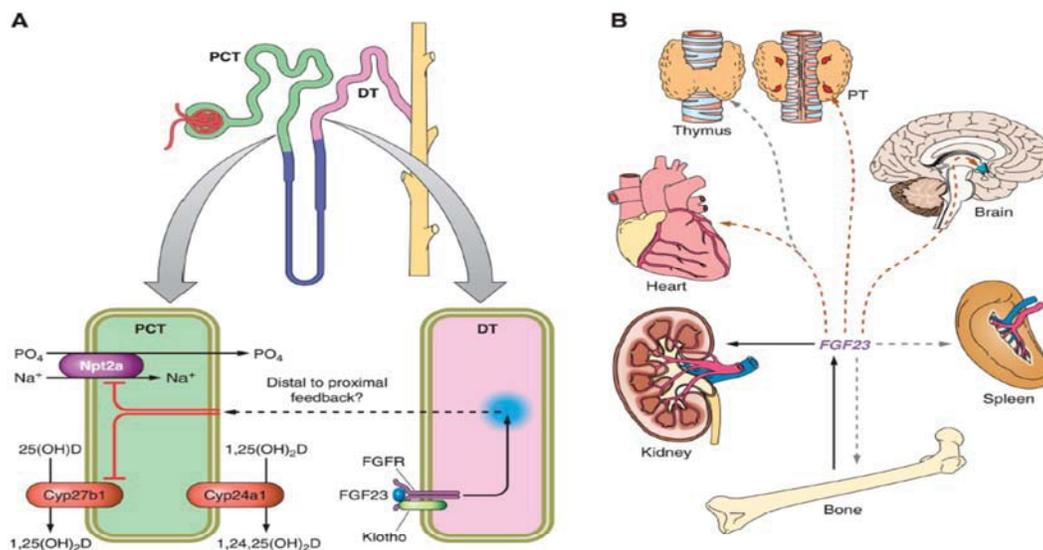


FIGURE 2. Renal and extrarenal functions of FGF23. *A*: hypothetical distal to proximal feedback mechanism: FGF23 activates FGFR/Klotho complexes in the renal distal tubules (DT) leading to two predominant events in the proximal convoluted tubules (PCT): the inhibition of expression of Npt2a and the inhibition of Cyp27b1. As a consequence, phosphate reabsorption and 1,25(OH)₂D production are respectively decreased. Additionally, the increase in Cyp24a1 expression contributes to lowering 1,25(OH)₂D levels due to increased catabolism of 1,25(OH)₂D. *B*: extrarenal targets of FGF23 are tissues that express FGFR and Klotho, including kidney, but also parathyroid gland (PTG), heart, and brain (brown arrows) or tissues that express the FGFR alone such as thymus, spleen, or bone (gray arrows), indicating possible paracrine effects of FGF23. Possible hormonal regulation loops are yet to be discovered.

In vitro and in vivo pharmacodynamics studies were conducted to evaluate the mode of action of burosumab and to provide evidence of potential efficacy.

An in vitro binding study showed that burosumab had similar high binding affinity ($K_D \approx 10^{-11}$ mol/L) to human, cynomolgus monkey and rabbit FGF23 (Study r-12-0326). Burosumab was also shown to be cross-reactive with recombinant forms of monkey and human FGF23 but not mouse FGF23 (Study r-13-0026), and with plasma FGF23 from humans and monkeys but not dogs or rats (Study r-13-0027). These studies established that cynomolgus monkeys and rabbits are appropriate models for evaluating pharmacological and toxicological responses to burosumab.

Other in vitro studies showed that burosumab could inhibit signaling mediated by the FGFR/Klotho receptor complex. In a cell-based assay (Study d-11-816), burosumab (1-10000 ng/mL) inhibited rhFGF23 signaling in a concentration-dependent manner. In another cell based assay (Study r-13-0021), burosumab (10 ug/mL) inhibited signaling of human, monkey and rabbit FGF23, but not mouse or rat FGF23. Burosumab/FGF23 complex bound to recombinant human Klotho with a K_D value of 9.12×10^{-8} mol/L (Study r-14-0106) and to human Klotho expressing cells (Study r-14-0107), indicating that burosumab binds to the FGFR-binding N-terminal domain of FGF23. However, the C-terminal domain of FGF23 retains the ability to bind to α -Klotho. Accordingly, burosumab/FGF23 complex (1-10000 ng/mL, expressed as concentrations of human FGF23) inhibited FGF23 signaling in a cell-based assay by competing with unbound FGF23 for binding to α -Klotho (Study r-16-0342). The in vitro studies confirmed the claimed mechanism of action of burosumab.

In vivo single dose pharmacology studies were conducted in New Zealand rabbits and in adult or juvenile monkeys. In rabbits, burosumab (3-30 mg/kg, single dose, IV) increased serum phosphate and 1,25(OH)₂D levels, and decreased urinary phosphate and calcium levels (Study (b) (4) 07448). The mortality/unscheduled euthanasia observed in 3/8 rabbits in the 30 mg/kg group was probably due to acute renal failure caused by nephrocalcinosis. This was related to marked serum phosphorus elevations in normal burosumab-treated animals (see Toxicology section).

In adult monkeys (Study (b) (4) 07185/ (b) (4) 07309), burosumab (1-10 mg/kg, single dose, IV) caused significant increases in serum phosphorus, tubular maximal reabsorption of phosphate per glomerular filtration rate (TmP/GFR) and serum 1,25(OH)₂VitD levels. The T_{max} for 1,25(OH)₂VitD was 1 day. The T_{max} for serum phosphorus was Day 2-3 at 0.03-1 mg/kg, and Day 3-8 at higher doses of 3-10 mg/kg. Serum 1,25(OH)₂VitD returned to baseline within 2-3 days, while serum phosphorus remained increased for an extended time. The later time of the serum phosphorus increase may be due to a transient increase in osteocyte FGF23 expression by 1,25(OH)₂VitD.

Study (b) (4) 07190 showed that the minimum effective dose in adult monkeys was **0.1 mg/kg** for increases in serum phosphorus and **0.03 mg/kg** for increases in 1,25(OH)₂VitD (Figures 2 and 3 below). In another study in adult monkeys ((b) (4) 303-022) with single doses of 0.03, 0.3, and 3 mg/kg, it was shown that the extent and duration of the serum phosphorus and 1,25(OH)₂VitD

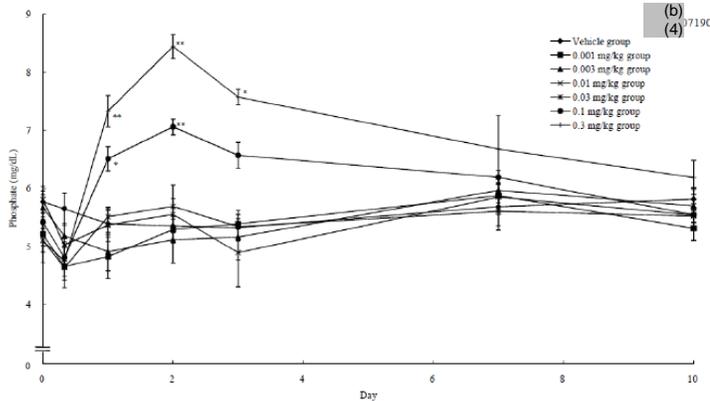
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responses were comparable upon IV and SC dosing. PK data from this study are described in ADME/PK Section 5.4 below.

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Figure 2 Study (b) (4) 07190

Figure 2.6.2.1.3.1.1: Effect of KRN23 IV on Serum Phosphorus Levels in Adult Cynomolgus Monkeys (Study No. (b) (4) 7190)



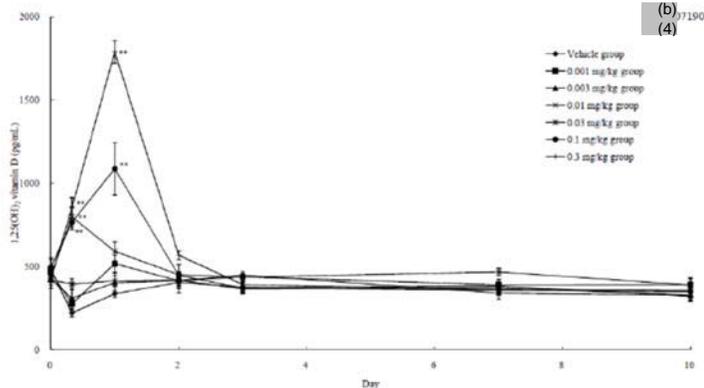
(n=4, mean ± SEM)

The broken lines (brown) indicate the normal reference range as the reference values.

*P<0.05, **P<0.01, significantly different from the vehicle

Figure 3 Study (b) (4) 07190

Figure 2.6.2.1.3.1.2: Effect of KRN23 IV on Serum 1,25(OH)₂D Levels in Adult Cynomolgus Monkeys (Study No. (b) (4) 7190)



(n=4, mean ± SEM)

**P<0.01, significantly different from the vehicle

In a study in juvenile monkeys with single IV doses of burosumab at 0.001, 0.003, 0.01, 0.03, 0.1 mg/kg (Study (b) (4) 303-021), elevations in serum phosphorus were observed at ≥ 0.03 mg/kg and increases in 1,25(OH)₂VitD were seen at ≥ 0.003 mg/kg. Thus, the minimally effective doses in juvenile monkeys were 3-fold and 10-fold lower for serum phosphorus and 1,25(OH)₂Vit,

respectively, than in adult monkeys. The T_{max} for the serum phosphorus increase (3-14 days) was larger in juvenile than in adult monkeys (<7 days).

The PK/PD of burosumab in male and female adult and juvenile monkeys upon Q2W dosing with 1 mg/kg (SC) for 14 weeks (7 doses) was evaluated in Study ^{(b) (4)} 303-116. Increases in serum IP were observed by 8-24h after dosing and phosphorus levels generally reached a peak by 3-5 days post dose, both after 1st and last dose in all treatment groups. Baseline serum phosphorus was higher in juveniles (5-6 mg/dL) vs adults (3-4 mg/dL). Maximum serum phosphorus values post dose were also higher in juvenile than in adult monkeys, but the difference between maximum and baseline values was the same for both age groups. Serum phosphorus increases were not affected by repeated burosumab administration and returned to pre-treatment levels during a 50-day recovery period. PK data from this study are described below (ADME/PK Section 5.4).

Attenuation of the serum phosphorus and 1,25(OH)₂vitD responses over time was observed in the 14-week rabbit and the 40-week adult monkey toxicity study in the absence of ADA development, but not in the 40-week juvenile monkey toxicity study or the 14-week monkey PK/PD study (^{(b) (4)} 303-116). Steady state was reached for the phosphorus response after approx. 3 months (trough) to approx. 6 months (peak) in the 40-week study. Clinical studies in adults also showed this phenomenon and stabilization of the phosphorus response appeared to occur after 12-14 weeks. The cause of this attenuation is unknown. The applicant suggested it may represent a homeostatic mechanism attempting to normalize serum phosphorus and 1,25(OH)₂D levels. An increase in free FGF23 concentrations due to increased production and/or reduced clearance may be responsible.

Overall, there were no meaningful changes in serum Ca or PTH after burosumab administration in animals, consistent with intact regulation of calcium metabolism.

Secondary Pharmacology

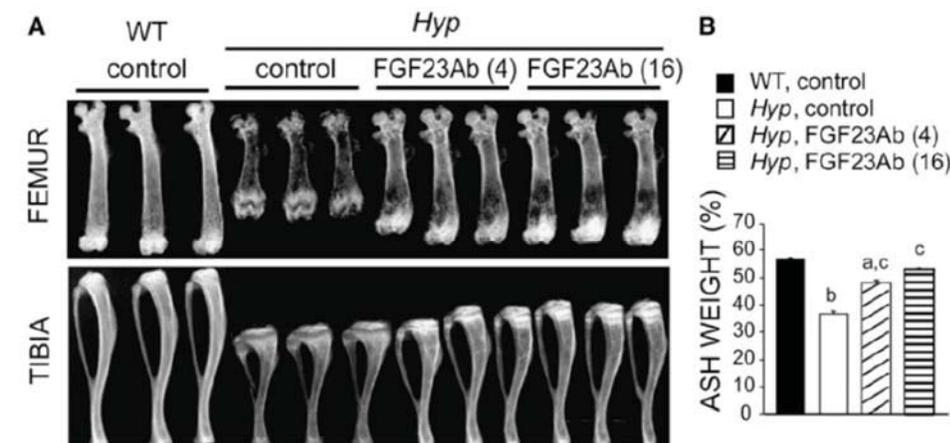
The Hyp mouse was used to test the hypothesis that anti-FGF23 mAbs could reverse the abnormalities associated with XLH. The Hyp mouse is a murine homologue of XLH with a deletion in the 3' region of the *Phex* (Phosphate-Regulating Gene with Homologies to Endopeptidases on the X-chromosome) gene. Similar to XLH patients, these animals have elevated serum FGF23 levels, and display hypophosphatemia, rickets and associated developmental abnormalities, and osteomalacia. Since burosumab does not bind to mouse FGF23, a murine anti-FGF23 antibody (Ab) was used in these studies.

In the first study (Aono et al. 2009), juvenile male Hyp mice treated with 4 weekly SC doses of a murine anti-FGF23 Ab (4 or 16 mg/kg) had significant dose-related elevations in serum phosphorus and 1,25(OH)₂D levels, which exceeded those in WT control mice at the 16 mg/kg dose. This was accompanied by increased renal expression of type IIa sodium-phosphate cotransporter (NaPiIIa). Anti-FGF23 Ab treatment caused a marked improvement of growth

retardation, elongation of femoral and tibial bones, and an improved columnar structure of proximal metaphyseal growth plates (Figure 4 below). The Ab also markedly reduced osteoid measures, increased relative mineralized bone volume in trabecular and cortical bones, and increased long bone ash weight. Increased 25(OH)VitD-1 α -hydroxylase and suppressed renal expression of (OH)2VitD-metabolizing 24-hydroxylase were also observed.

Figure 4 Hyp Mouse Radiographic Findings

Figure 2.6.2.1.3.1: X-ray Bone Radiographs of femur and tibia (A), and femoral ash weight (B)



(B) n=5-7, mean \pm SE

^a p<0.05 and ^b p<0.01 vs. WT control (Dunnett).

^c p<0.01 vs. Hyp control (Dunnett).

The numbers in parentheses refer to anti-FGF23 Ab dose given (mg/kg).

In the second study (Aono et al. 2011), adult male Hyp mice were treated with 8 weekly SC doses of murine anti-FGF23 Ab (4 or 16 mg/kg). Serum phosphorus and 1,25(OH)₂D levels were dose-dependently increased compared to control Hyp mice and also compared to WT mice at 16 mg/kg. Long bone length was not affected by anti-FGF23 Ab treatment but ash content was. Osteoid volume was reduced to almost similar values as in WT animals, suggesting normalization of bone mineralization. In the Hyp mice, grip strength of forelimbs and hind limbs and frequency of spontaneous movement were lower than in WT mice, possibly due to muscle weakness and bone pain similar to that observed in patients with hypophosphatemic rickets/osteomalacia. Treatment of Hyp mice with anti-FGF23 Ab gradually increased grip strength and increased the frequency of spontaneous movement in a dose-dependent manner.

The Hyp mouse studies supported the concept that the neutralization of excess FGF23 can improve hypophosphatemia, defective bone mineralization (rickets/osteomalacia), longitudinal bone growth, muscle weakness and spontaneous movement.

Safety Pharmacology

Safety pharmacology endpoints were incorporated in 14-day and 40-week repeat dose toxicity studies in adult and/or juvenile cynomolgus monkeys.

In the 14-week repeat dose toxicity study in adult monkeys (Study 6691-185), there were no arrhythmias, or effects on ECG, blood pressure or respiratory rate at IV doses up to 30 mg/kg Q2W.

In the 40-week repeat dose toxicity study in adult monkeys ((b) (4) 303-044), an increase in heart rate and depressed ST interval, but no effect on blood pressure was noted in males in the 30 mg/kg IV and/or SC groups. These changes were no longer present upon recovery. However, during the 13-week recovery period, low left ventricular end-diastolic and end-systolic volumes (EDV/ESV), low stroke volume (SV), and/or low ejection fraction (EF) were observed in males in the 30 mg/kg IV and SC groups. These findings were likely to be related to mineralization of cardiac fibers or vessels and/or the aorta tunica media associated with serum peak phosphorus levels > 8 mg/dL in the 30 mg/kg groups. In the 40-week juvenile monkey study ((b) (4) 303-020) no treatment-related changes in ECG parameters or blood pressure were noted. There were no signs of CNS effects in both monkey studies.

5.4. ADME/PK

This section focuses on pharmacokinetic(PK)/toxicokinetic (TK) parameters determined in rabbits and cynomolgus monkeys (adult, juvenile, or pregnant) after single and repeat dose IV or SC administration. Distribution, metabolism and excretion data were not specifically collected for this monoclonal antibody.

Single Dose

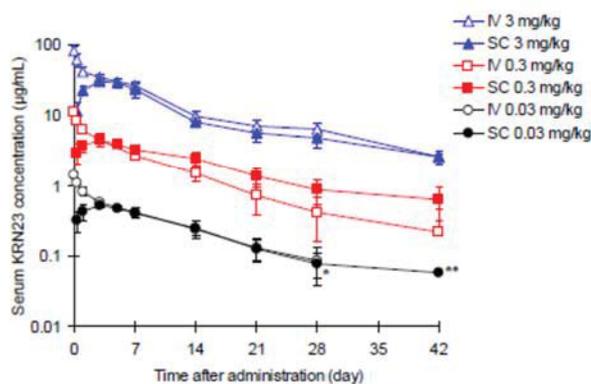
In a single IV dose study in male and female rabbits, at 0.03, 0.3, and 3 mg/kg, the serum concentration immediately after the end of dosing (C_0) and $AUC_{0-\infty}$ increased with dose (Study (b) (4) 052-086).

In a single IV dose study in male juvenile cynomolgus monkeys (0.001, 0.003, 0.01, 0.03, and 0.1 mg/kg), C_0 and $AUC_{0-\infty}$ increased in a dose-proportional manner between 0.01 and 0.1 mg/kg. $T_{1/2}$ ranged from 102 to 172 hours (Study (b) (4) 303-021).

In a single dose study in male adult cynomolgus monkeys with IV or SC doses of 0.03, 0.3, and 3 mg/kg, C_0/C_{max} and $AUC_{0-\infty}$ increased with dose with both dosing routes (Study (b) (4) 303-022) (Figure 5 below). $AUC_{0-\infty}$ values were similar for both administration routes. T_{max} ranged from 60 to 96 hours with SC dosing. $T_{1/2}$ ranged from 172 to 310 hours and was similar for the IV and SC routes of administration.

Figure 5 IV vs SC dosing in male adult monkeys (Study ^{(b) (4)} 303-022)

Figure 2.6.4.3.2.6.1: Serum Concentration Profile of KRN23 after Single Intravenous/Subcutaneous Dose Pharmacokinetics and Pharmacodynamics Study of KRN23 in Cynomolgus Monkeys (Study No. ^{(b) (4)} 303-022)



Mean ± SD (n=4, *n=3, **n=2)

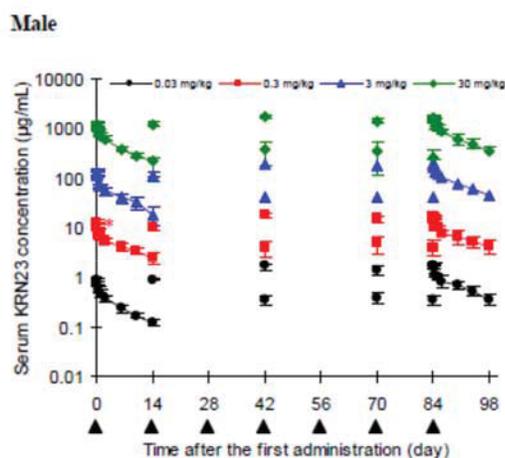
Multiple Dose

In a 14-week repeat dose IV toxicity study in rabbits (Study ^{(b) (4)} 052-076) with Q2W doses of 0.03, 0.3, and 3 mg/kg, C_{max} increased dose-proportionally and AUC_{0-∞} increased slightly less than dose proportionally after the 1st dose. Clearance (CL) increased with dose, and was higher in females. T_{1/2} ranged from 121-157h in males, 94-134h in females, and was shorter at the highest dose. Slight increases in C_{max} and AUC_{0-∞} were observed after the 7th versus the 1st dose at 0.3 and 3 mg/kg but not 0.03 mg/kg. No significant differences between females and males were noted. No anti-drug antibodies (ADA), i.e., anti-burosumab antibodies, were detected in this study.

In a 14-week repeat dose IV toxicity study in adult cynomolgus monkeys (Study 6691-185) with Q2W doses of 0.03, 0.3, 3, and 30 mg/kg, AUC_{0-∞} after 1st and last dose increased in a dose-related manner (Figure 6 below). V_{ss} (volume of distribution at steady state), T_{1/2} and MRT (mean residence time) showed no obvious differences between dose levels, indicating that PK was linear in this dose range. T_{1/2} ranged from 208-279h in males, and 160-259h in females. C_{max} and AUC at the 0.03, 0.3 and 3 mg/kg doses were slightly larger after the final versus the first dose, indicating drug accumulation. V_{ss} values were similar to serum volume, suggesting that distribution was limited to serum. No significant differences in PK parameters between the sexes were noted. In contrast to the 14-week rabbit study (Study ^{(b) (4)} 052-076), ADA were detected in 2 animals in the 3 mg/kg group, resulting in decreased serum burosumab concentrations.

Figure 6 14-week repeat dose IV study in adult monkeys (Study 6691-185)

Figure 2.6.4.3.3.1: Serum Concentration Profile of KRN23 (IV): 14-Week, Repeat-Dose Study in Adult Cynomolgus Monkeys (Study No. (b) (4) 6691-185)



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In a 40-week repeat-dose toxicity study in adult cynomolgus monkeys (Study (b) (4) 303-044) with Q2W doses of 0.03, 0.3, 3, and 30 mg/kg IV or 30 mg/kg SC, C_{max} and AUC increased proportionally with dose up to 3 mg/kg, but the increase was less than dose-proportional from 3 to 30 mg/kg. Burosumab accumulation (AUC_{0-τ} increase) was observed at the 0.03 and 0.3 mg/kg between the 1st and 20th dose, and at the 3 mg/kg dose between 1st and 7th dose, but not at the 30 mg/kg dose. T_{max} upon SC dosing was unchanged throughout the study. There were no obvious or consistent differences in PK parameters between males and females with IV dosing. However, AUC_(0-τ) was larger at the IV vs. the SC dose of 30 mg/kg in both sexes. ADAs were detected in 1 male in the 30 mg/kg IV group. In this animal, exposure to burosumab was decreased after the final 20th dose compared with that of other animals in this group and serum IP and 1,25(OH)₂D did not increase at the later stages of the dosing period.

In a 40-week repeat dose toxicity study in juvenile cynomolgus monkeys (Study (b) (4) 303-020) with Q2W doses of 0.03, 0.3, and 3 mg/kg IV or 3 mg/kg SC, C_{max} and AUC increased approx. dose-proportionally. T_{max} with 3 mg/kg SC was unchanged throughout the study. Accumulation (AUC_{0-τ} increase) was observed between 1st and 7th (or 20th) dose at all dose levels. There were no apparent differences in PK parameters between sexes. However, AUC was larger in both sexes at the IV vs. the SC dose of 3 mg/kg. C_{max} and AUC_{0-τ} at 0.03, 0.3 and 3 mg/kg were smaller in juvenile than in adult monkeys. ADAs were not detected in any animal.

A 13-week PK/PD study was performed in male and female adult and juvenile cynomolgus monkeys with Q2W SC doses of 1.0 mg/kg (Study (b) (4) 303-116). After the 1st dose, T_{max} was 60-72 hours and C_{max} ranged from 14.5-18.7 mcg/mL. T_{1/2} ranged from 240-366 hours and was shorter in juveniles than adults. T_{1/2}, CL/F or CL_{ss}/F, and V_z/F did not change after multiple doses. Exposure was considered to reach steady state by the 3rd dose. AUC_{0-∞} after 1st dose was 6000-9000 μg.h/mL. AUC_{0-∞} after the 1st dose and AUC_{0-t} after the 7th dose were very similar, indicating that earlier doses did not affect the PK of subsequent doses. PK parameters did not differ significantly between juveniles and adults, or males and females. Lower AUC was observed in juvenile vs adults monkeys in other monkey studies conducted with different IV burosumab dose levels. ADAs were not detected in any animals.

In an enhanced pre- and post-natal development (ePPND) monkey toxicology study ((b) (4) 303-043), the PK of burosumab was evaluated in dams, fetuses, and offspring. Pregnant cynomolgus monkeys were administered Q2W IV doses of 0, 0.3, 3 or 30 mg/kg from GD20 to either GD133 or delivery. Dams were terminated at weaning, and offspring was observed through PND360. Exposure in dams increased with dose. AUC_{0-t} after the 9th dose was slightly larger but similar to AUC_{0-∞} after the 1st dose, indicating that repeat dosing did not affect PK. T_{1/2} in dams varied from 14.6 days at 0.3 mg/kg to 16.1 days at 30 mg/kg. The plasma concentration (C_{pl}) in fetuses on GD 133 was approximately 0.25 times the C_{pl} in dams. C_{pl} in offspring on PND 5 increased with dose level, and decreased during the postnatal period with a T_{1/2} of 15.2 days at 0.3 mg/kg to 21.3 days at 30 mg/kg. C_{pl} values in offspring were 0.7-3.8 times those observed in dams at 0.3-30 mg/kg, suggesting significant in utero exposure particularly at 30 mg/kg. ADA were not present in any dams during the gestation period, but were detected in 2 dams during the lactation period. ADA were also not detected in any fetuses or offspring.

5.5. Toxicology

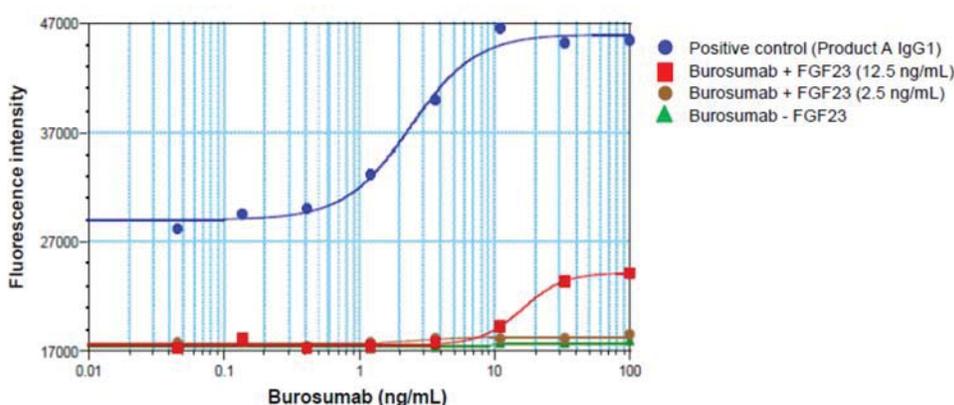
5.5.1. General Toxicology

ADCC assay

An in vitro antibody-mediated cellular cytotoxicity (ADCC) test revealed a potential hazard of antibody dependent cellular cytotoxicity. The assay utilized human HEK#18 target cells (kidney cells) and KC9775 effector cells (natural killer cells). Burosumab binds to the N-terminal part of

FGF23 which is involved in FGFR1 binding. The ADCC-type cytotoxicity would be mediated by binding of the C-terminal part of FGF23 in the burosumab-FGF23 complex to α -Klotho. The response was dose-related in the 10-100 ng/mL burosumab range and was evident in the presence of 12.5 ng/mL but not 2.5 ng/mL FGF23 (Figure 7 below). Concentrations of 100 ng/mL burosumab and 12.5 ng/mL FGF23 are similar in nM units (ca. 0.68 and 0.45nM, respectively), but both are lower than in vivo circulating total serum/plasma concentrations, in XLH patients and/or animals. However, tissue concentrations of both factors are unknown and may be smaller than those measured in serum/plasma. The potential relevance of the data is discussed in Section 5.6.

Figure 7 in vitro ADCC assay



Rabbit

In single dose IV studies in the New Zealand White (NZW) rabbit ((b) (4)-052-086, (b) (4)07448), the main effects included increases in serum phosphorus and 1,25(OH)₂VitD at doses ≥ 0.3 mg/kg, and ectopic mineralization in multiple soft tissues at doses ≥ 1 mg/kg (Table 4 below). Mortality was observed in 3/8 animals at 30 mg/kg (Study (b) (4)07448), and in 1/10 animals at 3 mg/kg (Study (b) (4)052-086). Mortality occurred in animals with extensive soft tissue mineralization and was probably due to nephrocalcinosis/renal failure.

A 14-week repeat-dose toxicity study ((b) (4)052-076) was conducted in NZW rabbits (N=4/s/g) with Q2W IV doses of **0, 0.03, 0.3, 3 mg/kg**. Vehicle was 10 mmol/L Sodium Glutamate, 262 mmol/L D-Sorbitol, 0.5 mg/mL Polysorbate 80, pH5.5. The main effects included pulsatile increases in serum phosphorus and 1,25(OH)₂VitD with peak levels 4 days and 1-2 days after dosing (respectively), increases in Ca concentrations and ectopic mineralization. One 3 mg/kg male with extensive tissue mineralizations died on Day 6 probably due to nephrocalcinosis. Ectopic mineralization was also observed in other 3 mg/kg animals in multiple soft tissues (e.g. kidney, heart and aorta). Other toxicities (e.g., serum BUN increase, inflammation of kidney, lung, heart/aorta) were likely at least partly related to the soft tissue mineralizations. The

hematology changes are consistent with a proposed role for FGF23 in hemato- and lymphopoiesis (Martin et. al., 2012). Ectopic mineralization was observed in animals that had peak serum phosphorus concentrations ≥ 8.5 mg/dL. The NOAEL was 0.3 mg/kg, based on ectopic mineralization and mortality.

The sponsor suggested that the high normal serum Ca levels (14-15 mg/dL vs. 9-11 mg/dL in monkeys and humans) may have caused more extensive soft tissue mineralization in rabbits as compared to monkeys. This was supported by the mineralization data from 3 mg/kg groups in the 14-week rabbit and monkey studies.

Table 4 Rabbit single dose and 14-week repeat dose toxicity studies

	Type of study	Doses (mg/kg)	Major findings	AUC _{0-14d} (at final dose) (µg.h/mL)
(b) (4) 07448 (Non-GLP, pharmacology study)	Single dose	3, 10, 30 mg/kg (IV) N=8 males/g	3-30 mg/kg: Serum IP and 1,25(OH)2VitD increases (PD effect) 30 mg/kg: Mortality in 3/8 due to renal failure/nephrocalcinosis 30 mg/kg: BUN and creatinine increases; kidney calcification at serum [IP] of 8-39 mg/dL	-
(b) (4) 052-086 (GLP)	Single dose Sacrifice on Day 14 or 35	0, 0.03, 0.3, 3 mg/kg (IV) N=10 or 8/s/g	0.3-3 mg/kg: IP increase in serum/urine (PD effect) 3 mg/kg: Mortality of 1/10M on Day 5 with Day 3 serum IP of 13 mg/dL due to renal failure/nephrocalcinosis 3 mg/kg: BW/FC decrease, BUN increase, mineralizations in kidney/ heart/ aorta/ other tissues on Day 14 and 35, testis degeneration in 1/4M (D35) NOAEL = 0.3 mg/kg (based on mortality)	-
(b) (4) 052-076 (GLP)	14-week study 7 doses, Q2W No recovery period	0, 0.03, 0.3, 3 mg/kg (IV) N=4/s/g	0.3-3 mg/kg: Serum IP increases (maximal on Day 3 post-dose), preceded by 1,25 (OH)2VitD increases. IP and 1,25(OH)2VitD effects were pulsatile and attenuated w time. 3 mg/kg: Mortality of 1/4 M on Day 5 due to renal failure/nephrocalcinosis. Serum IP on Day 3 was 15 mg/dL 3 mg/kg: BW/FC decreases 0.3 mg/kg: RBC, eosinophil decreases 3 mg/kg: Hb/Hct decreases, neutrophil increase, BUN/creatinine increases, Alb/Glob changes Histopathology: 0.3 mg/kg: Kidney mineralization (minimal) in 1/4M 3 mg/kg: Ectopic mineralization in kidney/ heart/ aorta/ lung/ parathyroid/ ovary/ muscle/ stomach; also lung edema/congestion; renal tubule regeneration/fibrosis; heart/aorta inflammation/necrosis/degeneration (M,F); parathyroid cell atrophy (F) NOAEL = 0.3 mg/kg (based on ectopic mineralization and mortality) AUC multiple at NOAEL = 0.5x	(0.03) 112 (0.3) 1270 (3) 11,875

Adult Monkey

14-Week Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study with Burosumab in Cynomolgus Monkeys with a 6-Week Recovery (Study No. 6691-185)

A 14-week repeat-dose toxicity study (Study 6691-185) was conducted in cynomolgus monkeys (N=4/s/g) with Q2W IV doses of **0, 0.03, 0.3, 3, 30 mg/kg**. Vehicle was 10 mmol/L L-histidine, 252 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80, 10 mmol/L L-methionine, pH 6.25. Reversibility was assessed after 6 weeks in the vehicle-treated and 30 mg/kg groups (N=2/s/g).

The main effects included dose-related increases in serum (OH)₂VitD and phosphorus and dose-related ectopic mineralization in multiple soft tissues (Table 5 below). The observed attenuation of the pharmacologic effect on serum phosphorus and VitD was unrelated to ADA formation. There were no ECG or BP effects. Hematology changes at 30 mg/kg may reflect a role of FGF23 in hemato- and lymphopoiesis. At 30 mg/kg, hyperostosis and increases in bone markers OC (Osteocalcin) and CTx (Collagen type 1 cross-linked C-Terminal telopeptide) indicated enhanced bone turnover. The cause of the decrease in bone-specific alkaline phosphatase (ALKP) at 0.3-30 mg/kg was unclear.

Ectopic mineralization was observed in multiple tissues but was particularly evident in kidney, lung, heart and aorta. It was still seen in most tissues after recovery and was also observed in additional tissues. Parathyroid cell changes were seen in 3 and 30 mg/kg males. Soft tissue mineralization occurred at peak serum P concentrations ≥ 7.8 mg/dL. NOAEL was 0.3 mg/kg. ADA were present in 2 males at 3 mg/kg.

Table 5 Adult Monkey 14-week Repeat Dose Toxicity Study

	Type of study	Doses (mg/kg)	Major findings	AUC _{0-14d} (at final dose) (ug·h/mL)
6691-185 (GLP)	14-week study 7 doses, Q2W 6-week recovery N=4-6/s/g	Dosing phase 0, 0.03, 0.3, 3, 30 mg/kg (IV) Recovery 0, 30 mg/kg (IV)	0.03-30 mg/kg: Serum 1,25(OH) ₂ VitD increases, and 0.3-30 mg/kg: Serum phosphorus increases (PD effects). Effects were pulsatile and attenuated over time. Tmax (IP) was 3 days post-dose, and Tmax 1,25(OH) ₂ D was 1 day post-dose 30 mg/kg: BW gain small decrease (M) 0.3-30 mg/kg: Bone-specific ALKP decrease 30 mg/kg: RBC decreases in M, neutrophil increase, BUN increase, urine IP increase Bone changes: 30 mg/kg: OC and CTx increases Histopathology: 3-30 mg/kg: Ectopic mineralization in kidney (also some at 0.3 mg/kg)/ aorta/ brain/ colon/ lung/ pituitary/ adrenal/ eye/ heart/ parathyroid/ sciatic nerve/ seminal vesicle/ stomach/ trachea; also parathyroid cellular changes (M) 30 mg/kg: Limb swelling, periosteal hyperostosis and tendon mineralization in 1/6M 3 mg/kg: ADA (neutralizing) in 2/4 male animals At end of recovery, remaining changes were BSAP decrease in males, OC and CTx increases in females, and ectopic tissue mineralization in both sexes NOAEL = 0.3 mg/kg (based on ectopic mineralization) AUC multiple at NOAEL = 0.8x	(0.03) 184 (0.3) 2460 (3) 25,829 (30) 221,921

A 40-Week Intermittent (Once Every 2 Weeks) Intravenous/Subcutaneous Dose Toxicity and Toxicokinetic Study with KRN23 in Cynomolgus Monkeys with a 13-Week Recovery (Study (b) (4) 303-044)

A 40-week repeat-dose study was conducted in adult cynomolgus monkeys (4-8 years, 2.5-6.9 kg, N=4/s/g) with Q2W doses **0, 0.03, 0.3, 3, 30 mg/kg (IV), 30 mg/kg (SC)**. Vehicle was 10 mmol/L L-histidine, 252 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80, 10 mmol/L L-methionine, pH 6.25. Reversibility was assessed after 13 weeks in vehicle-treated and 30 mg/kg IV/SC groups (N=4/s/g). FGF23 concentrations ranged from 11 to 89 pg/mL prior to dosing.

The main findings included dose-dependent pulsatile increases in serum phosphorus and 1,25(OH)₂VitD, with peak levels at 4-7 days (Figure 8 below) and 2 days post-dosing, respectively, and dose-related ectopic mineralization in multiple soft tissues (Table 6 below). Peak serum IP values were **4.5 - 5.7 - 7.3 - 9.4 - 11.1 - 10.8 mg/dL** in 0 - 0.03 - 0.3 - 3 - 30 mg/kg

IV – 30 mg/kg SC groups, respectively, and were observed 4 days after the 1st dose. The phosphorus and 1,25(OH)₂VitD increases attenuated over time, but were still observed at end of study. The effects were more pronounced in males, even though exposure (AUC) in males was smaller than in females.

Swelling in extremities/limbs was observed in one 3 mg/kg male (hand) and in several 30 mg/kg IV and SC animals and was accompanied by abnormal gait. One 30 mg/kg (IV) male was euthanized in Wk 31 due to ensuing lateral position. The swelling was evident as accumulated material upon X-ray, swelling and milk white mass surrounding the bone upon necropsy, and mineralization of connective tissue (subcutis/muscle/articular capsule). One 0.3 mg/kg male with relatively high serum phosphorus levels also exhibited swelling, milk white mass and connective tissue mineralization in the foot.

The clinical pathology changes, e.g. ALKP and BUN increases, may have been related to FGF23 neutralization or secondary to ectopic mineralization. The hematology and spleen findings were consistent with a role of FGF23 in hemato- and lymphopoiesis.

The cardiac effects in 30 mg/kg males were probably secondary to cardiac mineralization in the presence of high serum phosphorus levels. They are also discussed in the safety pharmacology section of this review. The significance of the tracheal/lung perichondrocyte basophilic change was unclear but may also have reflected mineralization. No effects on teeth were reported.

Incidences and severities of tissue mineralizations were dose-related with minimal effects in kidney, lung and testis (rete testis and seminiferous tubules) in a minority of animals at 3 mg/kg. However, one 0.3 mg/kg male with serum phosphorus values similar to those in the 3 mg/kg group also showed moderate connective tissue mineralization. At 30 mg/kg, minimal to slight mineralization in the kidney was seen in all animals, while in other tissues (lung, heart and connective tissue) mineralization was more severe. In individual animals, kidney findings at 30 mg/kg other than mineralization (e.g., degeneration/necrosis, regeneration and fibrosis) were usually minimal and occurred only in animals with tubule mineralization. However, the severities of the mineralization and other findings were not always well correlated. Ectopic mineralization appeared more pronounced and persistent in males than in females. The threshold of peak serum phosphorus for ectopic mineralization was approx. 8.2 mg/dL.

Compared to the 14-week monkey study, incidences of tissue mineralizations were often higher at the same doses. Also, a few additional tissues were affected, although some tissues affected at 14 weeks showed no abnormalities at 40 weeks.

Bone turnover, bone thickness and mineral content/density were increased at 3 and/or 30 mg/kg. The cause of the femoral cortical BMD decrease and osteoid accumulation in 30 mg/kg males, accompanied by decreases in femur and vertebral bone strength was unclear. It may be due to suppression of autonomous FGF23 signaling in bone, or mineralization inhibition by the

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excessive increases in 1,25(OH)₂VitD (Martin et al, 2012). The bone changes may also be due to loss of independent non- α Klotho-mediated effects of FGF23 in the skeleton. The data indicate that excessive suppression of FGF23 in XLH patients is undesirable because of potential adverse effects on serum phosphorus and bone.

Histologic bone changes were observed at 30 mg/kg and included cortical bone basophilic changes, spongiform hyperostosis, Haversian canal dilatation and trabecular bone decrease.

ADA were detected in 1 male in the 30 mg/kg IV group, after Week 15. In this animal, AUC decreased and serum phosphorus and 1,25(OH)₂VitD did not increase in later stages of the dosing period.

The NOAEL in the 40 week monkey study was 0.3 mg/kg, based on the appearance of ectopic mineralization.

Figure 8 Serum Phosphorus in Adult Monkeys

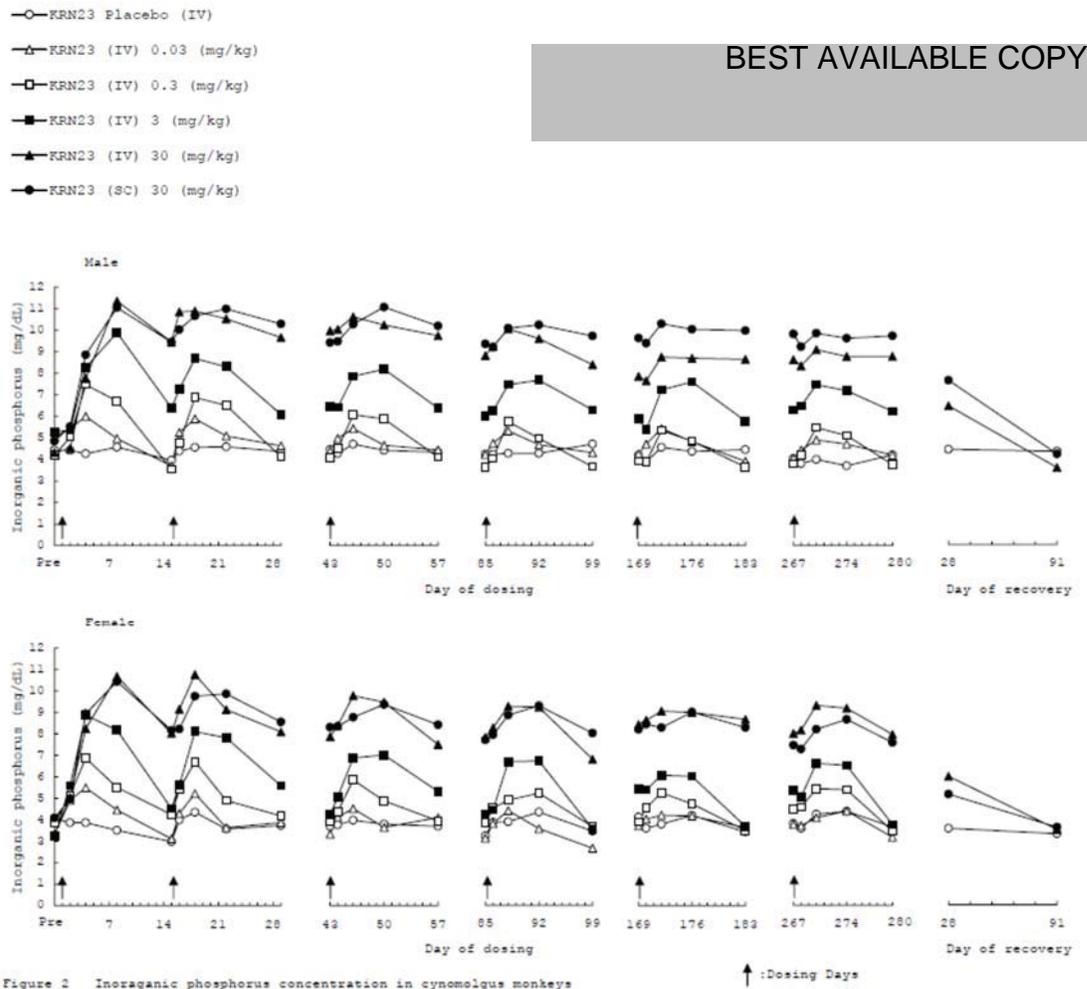


Table 6 Adult Monkey 40-week Repeat Dose Toxicity Study

Study #	Type of study	Doses (mg/kg)	Major findings	AUC _{0-14d} (at final dose) (ug·h/mL)
(b) (4) 303-044	40-week study	Dosing phase 0, 0.03, 0.3, 3 (IV), 30 (IV or SC) mg/kg	0.03-30 mg/kg: Serum phosphorus and 1,25(OH) ₂ vitD increases, and urine P excretion increase (PD effects). Effects were pulsatile and attenuated over time. Tmax (IP) was 4-7 days post-dose, and Tmax (OH ₂ D) was 2 days post-dose. Effects more pronounced in males.	(0.03) 337
(b) (4) GLP	20 doses, Q2W 13-week recovery N=4-8/s/g	Recovery 0, 30 (IV/SC) mg/kg	30 mg/kg: 1M euthanized D211 3-30 mg/kg: Swelling in extremities, abnormal gait 30 mg/kg: HR increase and ST decrease; and in recovery period cardiac volume/output decrease in males 3-30 mg/kg: RBC and lymphocyte decreases; platelet changes	(0.3) 2605 (3) 28,100 (30IV) 164,000 (30SC) 141,000

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Study #	Type of study	Doses (mg/kg)	Major findings	AUC _{0-14d} (at final dose) (ug·h/mL)
			<p>3-30 mg/kg: Albumin, protein, A/G, creatinine decreases; ALKP and BUN increases (males)</p> <p>0.3-30 mg/kg: Swelling of extremities, bone thickening & rough surface, milk white mass around bones, accumulated material upon X-ray in females only at 30 mg/kg</p> <p>30 mg/kg: adrenal and kidney weight increases</p> <p>Histopathology: 0.3-30 mg/kg: Ectopic mineralization</p> <ul style="list-style-type: none"> • connective tissue at ≥0.3 mg/kg (1 male with serum phosphorus similar to 3 mg/kg group) • kidney/ lung/ testis seminiferous tubules at ≥3 mg/kg • aorta/ eye vessel/ heart/ liver/ sciatic nerve/ muscle/ spinal cord/ stomach/ rete testis at 30 mg/kg <p>3-30 mg/kg:</p> <ul style="list-style-type: none"> • kidney de/regeneration/ fibrosis/ necrosis/ inflammation concomitant with mineralization • trachea/lung perichondrocyte basophilic change • spleen lymphocyte decrease germinal center <p>Bone changes 0.3-30 mg/kg:</p> <ul style="list-style-type: none"> • OC and CTx (bone turnover marker) increases <p>30 mg/kg:</p> <ul style="list-style-type: none"> • Femur: Cortical area/circumference/BMC increases; cortical BMD increase in females but decrease in males • Femur osteoid increase, and femoral and vertebral strength decreases in males • Histology: Cortical bone basophilic changes (subperiosteal/Haversian canal), spongiform hyperostosis, Haversian canal dilatation (M,F); trabecular bone decrease (M) <p>ADA (neutralizing) in 1/8 30 mg/kg (IV) male</p> <p>At end of recovery, remaining changes included OC and CTx increases, bone changes including bone strength decrease, limb/tissue swelling and ectopic mineralization</p> <p>NOAEL = 0.3 mg/kg (based on ectopic mineralization)</p> <p>AUC multiple at 0.3 mg/kg NOAEL = 0.9x</p>	

Table 7 Toxicokinetics in 40-week Adult Monkey Study

Table 2.6.6.3.3.4: Toxicokinetic Parameters: Repeat-Dose 40-Week Toxicology Study in Adult Cynomolgus Monkeys

Dose (mg/kg)	Male				Female			
	1st Dosing		7th Dosing	20th Dosing	1st Dosing		7th Dosing	20th Dosing
	AUC _{0-∞} (µg·h/mL)	AUC ₀₋₃₃₆ (µg·h/mL)	AUC ₀₋₃₃₆ (µg·h/mL)	AUC ₀₋₃₃₆ (µg·h/mL)	AUC _{0-∞} (µg·h/mL)	AUC ₀₋₃₃₆ (µg·h/mL)	AUC ₀₋₃₃₆ (µg·h/mL)	AUC ₀₋₃₃₆ (µg·h/mL)
0.03 (IV)	228	159	267	376	202	141	232	298
0.3 (IV)	1650	1270	1850	2300	1790	1270	2850	2910
3 (IV)	29800	20600	33000	33000	20100	13800	22200	23200
30 (IV)	216000	154000	194000	137000	194000	125000	204000	190000
30 (SC)	185000	123000	120000	106000	180000	81200	142000	175000

Mean (n=4 to 8)

Juvenile Monkey

A 40-Week Intermittent (Once Every 2 Weeks) Intravenous/Subcutaneous Dose Toxicity and Toxicokinetic Study with KRN23 in Juvenile Cynomolgus Monkeys with a 13-Week Recovery (Study (b) (4) 303-020)

A 40-week repeat-dose study was conducted in juvenile cynomolgus monkey (6-7 months, 1-1.1 kg, with Q2W doses of **0, 0.03, 0.3, 3 mg/kg (IV), 3 mg/kg (SC)**, N=8/s/g (control and 3 mg/kg), or 4/s/g (other groups). Vehicle was 10 mmol/L L-histidine, 252 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80, 10 mmol/L L-methionine, pH 6.25. Reversibility was assessed after 13 weeks in vehicle-treated and 3 mg/kg IV/SC groups (N=4/s/g). Serum FGF23 concentrations ranged from 20 to 95 pg/mL 14 days prior to dosing. Serum phosphorus in controls was 7.6 mg/dL on Day -7, decreasing to 5.6 mg/dL at end of study.

The main findings included dose-dependent pulsatile increases in serum phosphorus and 1,25(OH)₂VitD at doses ≥0.03 mg/kg, with peak levels at 3 days (Figure 9 below) and 1 day after dosing, respectively, and ectopic mineralization in soft tissues at 3 mg/kg (Table 8 below). Peak serum phosphorus values were **7.6 - 7.6 - 8.8 - 10.1 - 9.6 mg/dL** in 0 - 0.03 - 0.3 – 3IV - 3SC mg/kg groups, respectively, and were observed 4 days after 1st, 2nd or 4th dose. After 6-8 weeks, the phosphorus and 1,25(OH)₂VitD increases started attenuating but were still elevated above normal range levels in the 3 mg/kg groups at end of study.

There were 3 non-treatment-related premature deaths. One male (3 mg/kg, SC) was euthanized in Wk 33, due to moribundity probably related to parasite infection. Also, one male (3 mg/kg, IV) and one female (3 mg/kg, IV) died in Wks 29 and 33, respectively. The applicant considered these deaths were due to tympanites (distended GI tract) which was observed in both animals, but the underlying cause of their deaths was not clear.

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Two 3 mg/kg males (one IV, one SC) exhibited swelling in extremities (hand or foot), which manifested as accumulated material on X-ray, milk white mass upon necropsy, and mineralization of connective tissue in subcutis/muscle in histopathology. These males survived until the scheduled necropsy.

Minor clinical pathology changes e.g. RBC and ALKP decreases were treatment effects of unclear significance.

Ectopic mineralization was observed at 3 mg/kg in kidney, connective tissue, eyeball, lung, submandibular salivary gland, and muscle. Ectopic mineralization incidence was highest in kidney, and very low in all other tissues. Severity was usually rated as minimal. The peak serum phosphorus threshold for ectopic mineralization was approx. 10 mg/dL, i.e. higher than in adults (8.2 mg/dL). The higher threshold for mineralization is consistent with the higher need for phosphate during growth in juveniles vs adults. There were very few kidney findings other than the minimal mineralization. The significance of the minimal tracheal squamous metaplasia in two 3 mg/kg animals was unclear.

Increases in bone turnover were observed at ≥ 0.03 mg/kg (CTx) or ≥ 0.3 mg/kg (OC). Increases in total and cortical bone BMD, BMC and/or thickness were observed at ≥ 0.3 mg/kg, with more extensive effects in males than in females. Low osteoid thickness was seen in males at 3 mg/kg IV or SC, and increased osteoid thickness was observed in one male at 3 mg/kg SC. Growth plate thickness and femur length were unaffected. There were no effects on femoral or vertebral bone strength. Increases in bone resorption and in osteoclasts and/or osteoblasts were observed at 30 mg/kg.

The increase in cortical thickness of the femur occurred at pharmacologic doses, at or below the NOAEL dose for toxicity. Positive bone effects were also noted in adult monkeys and Hyp mice, but they occurred at lower doses in juvenile than adult monkeys (0.3-3 mg/kg vs 30 mg/kg), possibly because of higher serum phosphorus levels and higher skeletal activity in growing juvenile animals.

The NOAEL in the juvenile monkey study was 0.3 mg/kg in males and females based on ectopic mineralizations

Figure 9 Serum Phosphorus in Juvenile Monkeys

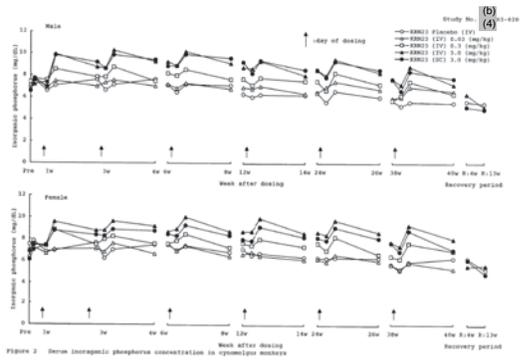


Figure 9 Serum inorganic phosphorus concentration in cynomolgus monkeys

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Table 8 Juvenile Monkey 40-week Repeat Dose Toxicity Study

Study #	Type of study	Doses (mg/kg)	Major findings	AUC _{0-14d} (at final dose) (ug·h/mL)
(b) (4) 03-020 (b) (4) GLP	40-week study 20 IV doses, Q2W 13-week recovery N=4-8/s/g	Dosing 0, 0.03, 0.3 (I), 3 (IV or SC) mg/kg Recovery 0, 3 (IV/SC) mg/kg	0.03-3 mg/kg: Serum phosphorus and (OH)2VitD increases, and urine phosphorus excretion increase (PD effects). Effects were pulsatile and attenuated over time. Tmax (phosphorus) was 4-7 days post dose, and Tmax 1,25(OH)2VitD was 2 days post-dose. Effects more pronounced in males. 3 mg/kg: 2M,1F died/euthanized, Wks 29-33 3 mg/kg: Swelling in hand/feet (M only) 3 mg/kg: RBC decrease 0.3-3 mg/kg: ALKP decrease, Ca excretion increase 3mg/kg: Swelling, milk white mass, X-ray accumulated material in hand/feet (M) Histopathology: 3 mg/kg: Ectopic mineralization <ul style="list-style-type: none"> kidney/ lung/ eye vessel/ submandibular gland/ connective tissue hand/foot, muscle 30 mg/kg: femur osteoclast and osteoblasts increases (M,F); trachea squamous metaplasia; spleen enlargement germinal center Bone changes: 0.03-3 mg/kg: <ul style="list-style-type: none"> OC and/or CTx (bone turnover) increases 0.3-3 mg/kg: <ul style="list-style-type: none"> Femur: Total BMD increase, cortical BMD/ BMC/ area/ thickness increases (M, F) 3 mg/kg: <ul style="list-style-type: none"> Osteoid thickness decrease (M, SC/IV) Osteoid thickness increase (M, SC) Histology: Increased bone resorption, increased osteoclasts, increased osteoblasts No ADA detected in any animal At end of recovery, remaining changes included OC and CTx increases and kidney/ eye/ connective tissue mineralization at 3 mg/kg NOAEL = 0.3 mg/kg (based on ectopic mineralization) AUC multiple at 0.3 mg/kg NOAEL = 0.34x	(0.03) 150 (0.3) 1870 (3IV) 23,250 (3SC) 18,450

Table 9 Toxicokinetics in 40-week Juvenile Monkey Study

Table 2.6.6.3.4.4: Toxicokinetic Parameters: Repeat-Dose 40-Week Toxicology Study in Juvenile Cynomolgus Monkeys

Dose (mg/kg)	Male				Female			
	1st Dosing		7th Dosing	20th Dosing	1st Dosing		7th Dosing	20th Dosing
	AUC _{0-∞} (µg·h/mL)	AUC ₀₋₃₁₂ (µg·h/mL)	AUC ₀₋₃₁₂ (µg·h/mL)	AUC ₀₋₃₁₂ (µg·h/mL)	AUC _{0-∞} (µg·h/mL)	AUC ₀₋₃₁₂ (µg·h/mL)	AUC ₀₋₃₁₂ (µg·h/mL)	AUC ₀₋₃₁₂ (µg·h/mL)
0.03 (IV)	104	81.6	154	134	103	81.3	195	165
0.3 (IV)	1310	954	1930	1910	1400	888	1990	1830
3 (IV)	16500	13300	14200	23400	15500	11600	13800	23100
3 (SC)	13500	10600	15300	20700	11100	8240	15400	16300
Mean (n=4 to 8)								

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Mouse

Influences of anti-FGF23 antibody in wild-type and Hyp mice (Study (b) (4) 303-084)

A 14-day study was conducted in wild type (WT) C57BL/6J mice and B6.Cg-PhexHyp/J (Hyp) mice. Genotypically, Hyp mice are the murine equivalent of XLH. Male mice (N=12/grp, age WT 8-9 wks or Hyp 7-10 wks) were dosed SC with murine anti-FGF23 antibody “FN1/FC1” (0, 3, 10, 30 mg/kg) on Days 1, 4, 7, and 10. Vehicle was phosphate-buffered saline. Evaluations included limited clinical pathology, bone pQCT, and histopathology. No toxicokinetic analysis was performed. Serum phosphorus before dose initiation was 4.8-5.6 mg/dL in WT mice, and 1.8-2.1 mg/dL in Hyp mice. Body weight at dose initiation was approx. 23.5 g in WT mice and 17.5 g in Hyp mice. FGF23 levels on final day of acclimation were 75 pg/mL in WT mice and 1506 pg/mL in Hyp mice, confirming the Hyp mouse “XLH-like” abnormality.

The FGF23 antibody caused increases in serum phosphorus and 1,25(OH)₂VitD in both WT and Hyp mice, but both baseline and peak serum phosphorus levels were lower in Hyp mice (Table 10 and Figure 10 below). Dose-related ectopic mineralization was observed in both genotypes at all doses, but incidence and severity were lower in Hyp mice. In this 14-day study, the threshold of peak serum phosphorus for ectopic mineralization was approx. 10 mg/dL for both genotypes (Figure 10 below).

The mineralization was most likely due to the pharmacology of FN1/FC1 to increase serum phosphorus and 1,25(OH)₂VitD. Besides lung and kidney, which were affected in both genotypes, mineralization was also observed in heart and/or aorta in WT animals. In the WT animals, at 3 mg/kg only the kidney was minimally affected by mineralization, but at 10 mg/kg both lung and heart/aorta were affected more extensively and severely than kidney. Except for the mineralization, there were no adverse histopathology findings. An increase in osteoblastic

bone formation was observed in both WT and Hyp mice. Hyp mice had significant but non-dose-related increases in femoral length and total femoral bone mineral content and density.

The NOAEL was <3 mg/kg in both WT and Hyp mice, based on increased incidences of ectopic mineralization at 3 mg/kg. However, in the 3 mg/kg WT mice the incidence and severity of the kidney and lung mineralization was similar to that in the 10 or 30 mg/kg Hyp mice. In that respect, WT mice were approx. 10 times more sensitive to mineralization than hypophosphatemic Hyp mice.

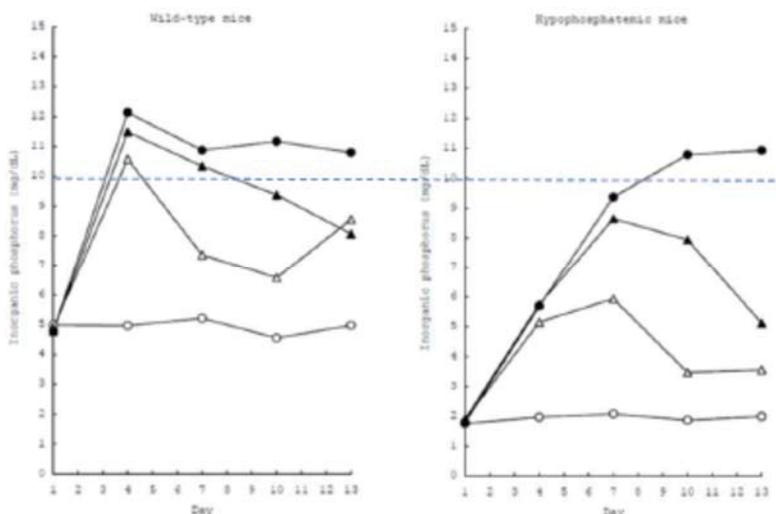
Table 10 WT and Hyp Mice 14-day Repeat Dose Study

		Wild type (WT)				Hyp			
Dose (mg/kg)		0	3	10	30	0	3	10	30
BW		-	-	↓ (>D4)	↓ (>D4)	-	-	-	-
Serum IP (mg/dL) (main grp)	Cmax (P)	5.2	10.6*	11.5*	12.1*	2.1	5.9	8.6*	10.9*
	Tmax (P)	D7	D4	D4	D4	D7	D7	D7	D13
OC (ng/mL)		47	61*	75*	98*	79	90*	93*	92*
CTx (ng/mL)		11	3.6*	9.3	14	26	27	21*	23
Femur (main grp)	Length (mm)	14.5	14.6	14.5	14.5	10.4	10.6	10.6	10.8*
	BMC (mg)	20	21	20	20	8.5	15*	16*	15*
	BMD (mg/cm ³)	522	565	536	526	295	402*	424*	395*
Histopathology (main grp)	Kidney mineralization	4/12 (minimal)	8/12 (minimal)	12/12 (minimal-slight)	12/12 (minimal-marked)	1/12 (minimal)	2/12 (minimal)	6/12 (minimal)	9/12 (minimal-slight)
	Lung mineralization	1/12 (minimal)	2/12 (minimal)	12/12 (minimal-marked)	12/12 (slight-marked)	1/12 (minimal)	3/12 (minimal)	3/12 (minimal)	7/12 (minimal)
	Heart/ aorta mineralization	0/12	0/12	9/12 (minimal-slight)	12/12 (minimal-moderate)	0/12	0/12	0/12	0/12
	Mineralization, all organs (kidney+lung + heart/aorta)	5/12	8/12	12/12	12/12	2/12	5/12 (similar to control WT mice)	7/12	9/12 (similar to 3 mg/kg treated WT mice)

*Statistically significant effects (**bold**)

Figure 10 Plasma Phosphorus Concentrations in WT and Hyp mice

Figure 6: Plasma phosphorus concentrations in Wt and Hyp mice during 2-weeks of treatment with anti-FGF23 antibody*



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*0 mg/kg (open circles), 3 mg/kg (open triangles), 10 mg/kg (solid triangles), 30 mg/kg (solid circles); Dashed line represents circulating phosphorus threshold above which ectopic mineralization develops

5.5.2. Genetic Toxicology

Burosumab is a monoclonal antibody and is not expected to interact directly with DNA or other chromosomal material. Therefore, genotoxic carcinogenicity is not expected and genotoxicity studies were not performed.

5.5.3. Carcinogenicity

No carcinogenicity studies were performed with burosumab. Standard 2-year rodent carcinogenicity studies with burosumab are not feasible since burosumab does not bind rodent FGF23. However, an assessment of the carcinogenic potential of burosumab based on a weight-of-evidence approach was conducted. Considerations included the mechanism of action of burosumab, data from published literature, *in vitro* and *in vivo* proliferation data, and information from the repeat-dose animal toxicity studies.

Pharmacological inhibition of FGF23 can be associated with a variety of pathologies, including hyperphosphatemia and ectopic mineralization. However, an association of FGF23 antagonism with carcinogenesis has not been identified. Neither human hyperphosphatemic familial

tumoral calcinosis (HFTC) patients nor knockout FGF23 mice exhibit proliferative disorders. In fact, in both in vivo and ex vivo proliferation studies, cells from knockout FGF23 mice had a markedly reduced ability to proliferate. Effects observed in rabbit and monkey toxicity studies included increases in serum phosphorus, 1,25(OH)₂vitD, and ectopic mineralization in various tissues, consistent with the pharmacology of burosumab. There were no histologically identified proliferative lesions in any tissues in these toxicity studies.

Slight increases in osteoclasts and osteoblasts were noted in the 40-week juvenile monkey toxicity study at the high dose of 3 mg/kg. They were associated with increased serum phosphorus levels, increased bone resorption and formation, and positive effects on bone mineral density and content, rather than bone proliferative lesions. The increase in bone turnover is a desired effect of burosumab which in the presence of increased serum phosphorus leads to an improvement of skeletal mineralization in XLH. The associated bone cell increases are not considered adverse.

In conclusion, given the evidence from human HFTC patients, FGF23 knockout mice, ex vivo and in vivo assays, the lack of evidence of cell proliferation in repeat-dose toxicology studies, and the lack of genotoxicity, burosumab is not expected to be carcinogenic.

The Executive Carcinogenicity Assessment Committee was consulted by the Division regarding the Sponsor's carcinogenicity risk assessment on April 28, 2017, and concurred that carcinogenicity studies with burosumab are not needed.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

No dedicated fertility studies were conducted. In the repeat-dose toxicity studies of up to 40 weeks duration in cynomolgus monkeys, no adverse effects on female reproductive organs or changes in menstrual cycle were observed. Mineralization (minimal) of the seminiferous tubules was observed in adult monkeys at 3 and 30 mg/kg and of the rete testis at 30 mg/kg. However, semen analysis did not show a significant dose-related changes in any parameter. The testicular mineralization was likely related to the increase in serum phosphorus levels. The testicular findings do not indicate a significant concern for male fertility since were most likely related to the elevated serum phosphorus levels in the animals.

Embryo-Fetal Development

Separate EFD studies were not performed. However, an ePPND study was conducted in cynomolgus monkeys.

Prenatal and Postnatal Development

A study for effects of KRN23 on embryo-fetal and pre- and postnatal development when administered once every two weeks by intravenous injection to pregnant cynomolgus monkeys (enhanced design) (b) (4) 303-043

Reproductive toxicity was evaluated in an enhanced pre- and postnatal development study (ePPND) study in cynomolgus monkeys. In this study, burosumab was administered Q2W at IV doses of 0, 0.3, 3, 30 mg/kg to pregnant monkeys from GD20 to delivery (Main Component, N=20/grp) or C-section on GD133 (Satellite Component, 0 mg/kg N=6/grp and 30 mg/kg N=8/grp). Vehicle was 10 mmol/L L-histidine, 252 mmol/L D-sorbitol, 0.5 mg/mL polysorbate 80, 10 mmol/L L-methionine, pH 6.25. Fetuses in Satellite Component (0, 30 mg/kg) were examined on GD133, and offspring in Main Component (0, 0.3, 3, 30 mg/kg) was evaluated up to PND (postnatal day) 360. Conducting lab was (b) (4), GLP study. Dams were evaluated until weaning and necropsied on postnatal day (PND) 190-208.

Burosumab produced expected dose-dependent increases in serum phosphate (IP) and 1,25 (OH)₂vitD in all treated animals. Ectopic mineralization was observed in dams at 3 and 30 mg/kg, including placental mineralization in C-sectioned 30 mg/kg animals. Serum IP levels were higher in fetuses/offspring than in maternal animals (7.1 vs. 3.9 mg/dL at 0 mg/kg, LD5), and were increased dose-dependently in fetuses and offspring (up to 8.4 mg/dL at 30 mg/kg, LD5). Ectopic mineralization was not observed in fetuses at C-sectioning (0, 30 mg/kg) or in offspring on PND 360 (all doses). Bone increases were observed in 30 mg/kg dams and fetuses on GD133.

The main findings included an increased incidence of combined abortion and embryo/fetal deaths during the fetal development period (GD51-139) at 3 and 30 mg/kg vs. concurrent control, and an increase in abortion and embryo/fetal death in the total gestation period (GD20-139) at 30 mg/kg vs. both concurrent and historical controls (Table 11 below). The GD51-139 fetal losses were within the conducting laboratory historical control (HC) range, however the GD20-139 fetal loss at 30 mg/kg was outside of the HC range.

For the analysis of premature births, the applicant and the applicant's experts defined premature birth as a birth before or on GD149, which included dead births/stillbirths from GD140-GD149. Their analysis showed an increase in premature births at all doses vs concurrent control and an increase outside of the HC range for the conducting laboratory at 3 mg/kg (Table 8). When excluding stillbirths, the increase at 3 mg/kg was still outside the HC range (Table 11 below).

Table 11 Fetal losses in ePPND study in cynomolgus monkeys

Dose (mg/kg)	Abortions/embryo-fetal deaths				Still-births	Total losses	Premature birth (live/dead, through GD149) ^A	Premature birth (live, through GD149) ^B	AUC multiple ^D
	GD20-50	GD51-139	GD140-delivery	Combined (GD20-139)					
0 (control)	4/26 (15.4%)	1/22 (4.5%)	2/20 (10%)	5/26 (19.2%)	2/15 (13.3%)	7/26 (26.9%)	1/15 (6.7%)	0/15 (0%)	-
0.3	1/20 (5%)	1/19 (5.3%)	0/20 (0%)	2/20 (10%)	0/18 (0%)	2/20 (10%)	2/18 (11.1%)	2/18 (11.1%)	0.88x
3	2/20 (10%)	2/18 (11.1%)	3/20 (15%)	4/20 (20%)	3/16 (18.8%)	7/20 (35%)	5/16 (31.3%)	3/16 (18.8%)	7.3x
30	4/28 (14.3%)	4/24 (16.7%)	1/20 (5%)	8/28 (28.6%)	1/16 (6.3%)	9/28 (32.1%)	2/16 (12.5%)	2/16 (12.5%)	64x
Control background data (b) (4) (2000-2009)	10/177 (5.6%) (0-22.2%)	9/177 (5.1%) (0-16.7%)	13/177 (7.3%) (0-28.6%)	19/177 (10.7%) (0-22.0%)	14/158 (8.9%) (0-28.6%)	33/177 (18.6%) (13.3-37.5%)	8/158 (5.1%) (0-14.3%)	≤8/158 (≤5.1%) (0-≤14.3%) ^B	-

Apparent numerical increases vs. concurrent and/or historical controls are **bold-faced**

^A live birth before/on GD149 or live or dead birth (stillbirth) from GD140 through GD149 (Sponsor's analysis)

^B live birth before/on GD149 (control background data for premature ≤GD149 live-only births are not available from (b) (4))

^C live birth from GD140 through GD154 (control background data from Oneda et al, 2012)

^D AUC in pregnant monkeys at 9th dosing vs. AUC(0-τ) at 1 mg/kg Q4W in adult humans (5,808,000 ng.h/mL) (Study UX023-CL303)

This reviewer also analyzed the data using the birth categories defined by Oneda et al (2012) (Table 12 below). An increase in premature pre-GD140 live birth incidence was observed at 3 and 30 mg/kg (Table 13 below). However, this was a small non-dose-dependent effect and did not exceed the HC range. An increase in preterm (GD130-GD154) live births was observed at all doses vs. concurrent controls and possibly exceeded the HC range at 30 mg/kg (Table 13). There was also an increase in combined premature and preterm births (<GD130-GD154) which may have exceeded HC at 30 mg/kg (Table 13). The premature infants at 3 and 30 mg/kg died on PND0 and PND1, respectively, which is consistent with the historical control mortality rate of 71% for these types of births (Oneda et al, 2012). One other neonate (control animal born on GD170, i.e. normal non-premature birth) died in the study on PND7. Live birth and viability

indices were not affected by burosumab treatment, indicating that the increased incidence of premature/preterm birth did not result in increased neonatal mortality in the study (Table 13).

Table 12 Historical Control Data for Birth Categories (Oneda et al, 2012)

Dose (mg/kg)	Premature births (live, pre-GD140)	Preterm births (live, GD140 through GD154)	Combined Premature + Preterm births (live, pre-GD140 through GD154)	Normal births (live, >GD154)
Frequency	3.3%	18.7%	22%	67%
Mortality	71%	10%	(Approx. 22%)	2.3%

Table 13 Premature, Pre-term, Normal Births Incidences; Live Birth/Viability Indices

Dose (mg/kg)	Premature births (pre-GD140)	Preterm births (GD140 through GD154)	Combined Premature + Preterm births (GD130 through GD154)	Normal births (>GD154)	Live Birth Index ^A	Viability Index >PND 1-7 ^B
0	0/15 (0%)	1/15 (6.7%)	1/15 (6.7%)	12/15 (80%)	13/15 (86.6%)	12/13 (92%)
0.3	0/18 (0%)	4/18 (22.2%)	4/18 (22.2%)	14/18 (78%)	18/18 (100%)	18/18 (100%)
3	1/16 (6.3%) (died on PND0)	3/16 (19%)	4/16 (25%)	9/16 (56%)	13/16 (81%)	12/13 (92%)
30	1/16 (6.3%) (died on PND1)	6/16 (38%)	7/16 (44%)	8/16 (50%)	15/16 (94%)	14/15 (93%)
Control background data (Oneda et al, 2012)	3.3 ± 4.3%	18.7±11.7% (live births from GD140-GD154) (Oneda et al, 2012)	N/A	67.3 ± 15.1%	N/A	N/A

Apparent numerical increases vs. concurrent and/or historical controls are **bold-faced**

^ALive birth index – number of live births/number of births (includes premature/preterm births)

^BViability Index > PND1-7 = number of infants alive on PND 8/number of live births

N/A Not available

Additionally, there was a dose-dependent decrease in gestation duration for all birth, live births and normal births at all doses, which was statistically significant for normal, i.e., non-

premature, >GD149, live births at 30 mg/kg (Table 14 below). However, none of the births occurred outside the HC range (2000-2009 ^{(b) (4)} database).

Table 14 Gestation Duration; Incidence of 140-160 Day Births

Dose (mg/kg)	Gestation duration (days)				Incidence of ≥GD140 live births with duration between 140 and 160 days ^E	Incidence of ≥GD140 all births with duration between 140 and 160 days ^E
	All births ^A ^{(b) (4)}	Live births ^B	Normal births ^C	Normal births ^D		
0 (control)	162 (143-175)	162 ±7.7 n=15	162	162	3/13 (23%)	4/15 (27%)
0.3	158 (142-167)	158 ±6.6 n=18	158	160	8/18 (44%)	8/18 (44%)
3	155 (133-168) ^Z	155 ±10.1 ^{ns} n=16	158	160	6/12 (50%)	8/16 (50%)
30	155 (139-165) ^Z	155 ±6.7 ^{ns} n=16	156	157*	11/14 (79%)	11/16 (69%)
Control background data ^{(b) (4)} (2000-2009)	160.8±6.3 days (143-174 days)	N/A	N/A	N/A	N/A	N/A

Apparent numerical increases vs. concurrent and/or historical controls are **bold-faced**

* statistically significant vs controls

^{ns} not statistically significant

^A live births, stillbirths, premature births (<GD140), preterm births (GD140 through GD154) and normal births (GD>154)

^B premature and non-premature (preterm and normal) live births ± SD

^C non-premature (preterm and normal) live births (≥GD140)

^D non-premature live births (>GD149)

^E data for live births only (from GD141 through GD159)

^F data for live and dead births (from GD141 through GD159)

[#] Two births, one at 3 mg/kg on GD133 and one at 30 mg/kg on GD139 occurred outside historical control range (143-174 days)

N/A Not available

There were no external, visceral or skeletal abnormalities (teratogenic effects) in the 30 mg/kg C-sectioned fetuses or in aborted fetuses from all dose groups. In the offspring, there were no treatment-related skeletal abnormalities or variations, and there were no effects on morphological, functional or behavioral development.

Burosumab AUC in dams was dose-related, and comparable to that in non-pregnant monkeys. Burosumab was detected at GD 133 in serum of 30 mg/kg fetuses at 0.25x maternal concentrations indicating trans-placental transport. Serum concentrations in offspring were also dose-related. Burosumab was eliminated slower in offspring than in dams, so that serum concentrations were 0.7x-1.7x (PND 5) to 1x-3.8x (PND 63) those in maternal animals, with higher levels in offspring vs maternal animals as time progressed. ADA were detected in 2 dams at 30 mg/kg during lactation, but not in fetuses or offspring.

Two NOAELs were reported by the conducting laboratory (b) (4). The NOAEL of 0.3 mg/kg was for toxicity and reproductive function in dams, based on mineralization at 3 and 30 mg/kg and increase in <GD149 premature births including stillbirths at 3 mg/kg. The NOAEL of 3 mg/kg was for pre- and postnatal development in fetuses and offspring, based on increased abortions and embryofetal deaths during fetal development and total gestation periods at 30 mg/kg. The applicant did not totally agree with this and concluded based on two expert's opinions and their own additional analyses that the treatment-relatedness of the increase in abortions and embryo-fetal losses at 30 mg/kg was equivocal. However, they agreed that the slight decreases in gestation period in all dose groups may have been related to burosumab treatment and to placental mineralization, and may have been associated with the increase in premature (pre-GD149, live and dead) births at 3 mg/kg.

This reviewer concludes that the increase in combined abortions and embryofetal deaths in the GD20-139 period at 30 mg/kg appeared to be treatment-related (Table 11 above). Also, using the definitions of premature and preterm birth by Oneda et al (2012) (Table 12 above), there appeared to be a treatment-related increase in preterm births (GD140-154) and combined premature and preterm births (<GD140-154) at 30 mg/kg (Table 13 above). The decrease in gestation duration also appeared to be treatment-related with significant and/or marked effects at 30 mg/kg (Table 14 above).

The decrease in gestation duration and the corresponding increase in preterm and/or premature births was not associated with adverse developmental or behavioral consequences. The increase in preterm/premature births at 30 mg/kg may represent an adverse treatment effect because an increased incidence in these births would generally be expected to be associated with an increased risk of neonatal death, as confirmed by the early deaths of both pre-GD140 premature infants (Table 13 above). Although the limited available data did not clearly indicate an association between placental mineralization and fetal loss, the treatment-related reproductive findings may nevertheless have been related to the development of placental mineralization in the non-XLH normophosphatemic monkeys.

The clinical relevance of the reproductive findings in the monkey study is not clear. Relatedness of the findings to the increase in serum phosphorus and placental mineralization in the non-XLH monkeys would suggest unlikely clinical relevance in the intended XLH patient population.

5.5.5. Other Toxicology Studies

Local tolerance

Burosumab was locally well tolerated by IV and SC administration. No gross or histopathological abnormalities were observed at the IV infusion or SC injection sites in the 40-week repeat dose toxicity studies in adult or juvenile cynomolgus monkeys.

Tissue Cross-Reactivity

Tissue cross-reactivity was assessed in vitro in human, rabbit, and cynomolgus monkey tissues by immunohistochemically assessing FITC-burosumab staining/binding. Specific FITC-burosumab staining was not observed in normal human, rabbit, or cynomolgus monkey tissues. Bone was not included in the tissue panel. No potential target organs of toxicity caused by binding of burosumab were identified. However, since this assay was carried out in the absence of FGF23, it was not adequate to identify pharmacological or toxicological target tissues based upon binding of burosumab-FGF23 complex to either FGFR or α -Klotho.

5.5.6 Toxicology Studies: Exposure Multiples

Table 15 below shows all AUC(0-t) values after the last dose in rabbit and monkey toxicity studies of 14- and 40-week duration. NOAEL values are bolded. It also shows animal vs. human exposure (AUC multiples, or “exposure margins”, for adults as well as children (1-4 yrs and 5-12 yrs, respectively).

Table 15 Summary of Exposure Margins in Repeat Dose Nonclinical Safety Studies

Table 1: Summary of Exposure Margins Achieved in Repeat Dose Nonclinical Safety Studies with Burosumab

Study No.	Species (Age)	Duration	Route	Dose (mg/kg)	AUC _{0-∞} (ng·h/mL) ^a		Exposure Margin (based on AUC) ^b					
					Male	Female	Male		Female			
							Adult	5 to 12 years	Adult	5 to 12 years		
(b) (4) 03-076	Rabbit (Adult)	14 weeks	IV	0.03	224000	222000	0.04	-	-	0.04	-	-
				0.3	2620000	2460000	0.45	-	-	0.42	-	-
				3	28000000	19500000	4.82	-	-	3.36	-	-
6691-185	Monkey (Adult)	14 weeks	IV	0.03	425000	284000	0.08	-	-	0.05	-	-
				0.3	4618000	5202000	0.80	-	-	0.90	-	-
				3	53326000	49910000	9.18	-	-	8.59	-	-
				30	431670000	45614000	74.32	-	-	78.51	-	-
				0.03 ^c	725000	596000	0.13	-	-	0.10	-	-
(b) (4) 03-044	Monkey (Adult)	40 weeks	IV	0.3 ^c	4600000	5820000	0.79	-	-	1.00	-	-
				3	66000000	46400000	11.36	-	-	7.99	-	-
				30	274000000	380000000	47.18	-	-	65.43	-	-
				30	2112000000	3500000000	36.50	-	-	60.26	-	-
				0.03	134000	165000	-	0.03	0.02	-	0.03	0.03
(b) (4) 03-020	Monkey (Juvenile)	40 weeks	IV	0.3	1910000	1890000	-	0.39	0.30	-	0.37	0.28
				3	23400000	23100000	-	4.78	3.62	-	4.72	3.58
				3	20700000	16300000	-	4.23	3.21	-	3.33	2.52
				30	2112000000	3500000000	-	36.50	47.18	-	60.26	65.43

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^b Bold indicates NOAEL; - not applicable
^c AUC_{0-∞} (ng·h/mL) at 7th dosing (Studies (b) (4) 03-076, 6691-185) and 20th dosing (Studies (b) (4) 03-044, (b) (4) 03-020)
^d NOAEL in Males
^e NOAEL in Females
^f AUC_{0-∞} as compared to simulated mean AUC_{0-∞} at 1 mg/kg Q4W in adults (5,808,000 ng·h/mL) and compared to Bayes exposure parameter in pediatric patients aged from 1-5 in Study UX023-205 (4,896,000 ng·h/mL), and in pediatric patients aged from 5 to <12 years in Study UX023-201 (6,456,000 ng·h/mL). Exposure levels were predicted under steady state conditions (PK and PK/PD Modeling and Simulations of burosumab in Children and Adults with X-linked Hypophosphatemia, July 2017). For Study No. (b) (4) 03-076, 6691-185, and (b) (4) 03-044, AUC was multiplied by a factor of 2 to account for the difference in dosing regimen (every 2 weeks) compared to UX023-CLL03 (every 4 weeks) for adults. The AUC was not adjusted for Study No. (b) (4) 03-020 since the pediatric human and juvenile monkey dose regimens were both every 2 weeks.

Table 16 below shows the safety margins calculated by the Sponsor for the long term general and reproductive toxicology studies.

Table 16 Summary of Safety Margins in Pivotal Nonclinical Studies

Table 2.4.6.1.1: Summary of Safety Margins Achieved in Pivotal Nonclinical Safety Studies with Burosumab

Study No.	Species (Age)	Duration	NOAEL/ other* (mg/kg)	Safety Margin (based on C _{max} ^b)	Safety Margin (based on AUC ^c)
(b) (4) 303-044	Monkey (Adult)	40 weeks	0.03 ^d	0.20 ^d	0.136 ^d
			0.3 ^e	1.54 ^e	1.00 ^e
(b) (4) 303-020	Monkey (Juvenile)	40 weeks	0.3 ^f	0.78 ^g 0.59 ^h	0.38 ^g 0.29 ^h
(b) (4) 303-043	Monkey (Pregnant)	GD20 to GD133/delivery	0.3	1.39 ⁱ	0.875 ⁱ
			3	12.1 ⁱ	7.33 ⁱ
			30	110 ⁱ	63.7 ⁱ

*No-Observed-Adverse-Effect-Level (NOAEL) for Study Nos. (b) (4) 303-044 and (b) (4) 303-020, defined as the dose level where elevation of serum phosphorus level was evident but did not result in ectopic mineralization. For Study No. (b) (4) 303-043, Lowest effect level (LOEL) for shortened gestation period is 3 mg/kg, NOAEL for pre- and post-natal development is 3 mg/kg and dose with placental mineralization is 30 mg/kg.

^bAs compared to simulated mean burosumab concentration at 1 mg/kg Q4W in adults (11,114 ng/mL) and compared to mean Bayes exposure in pediatric patients aged from 1- <5 years old in Study UX023-205 (16,195 ng/mL, with mean dose of 0.77 mg/kg) and in pediatric patients aged from 5 to <12 years in Study UX023-201 (21,349 ng/mL, with mean dose of 1.31 mg/kg). Exposure levels were predicted under-state conditions (PK and PK/PD Modeling and Simulations of burosumab in Children and Adults with X-linked Hypophosphatemia, July 2017).

^cAUC_{last} as compared to simulated mean AUC_τ at 1 mg/kg Q4W in adults (5,808,000 ng×h/mL) and compared to Bayes exposure parameters in pediatric patients aged from 1-5 in Study UX023-205 (4,896,000 ng×h/mL) and in pediatric patients aged from 5 to <12 years in Study UX023-201 (6,456,000 ng×h/mL). Exposure levels were predicted under-state conditions (PK and PK/PD Modeling and Simulations of burosumab in Children and Adults with X-linked Hypophosphatemia, July 2017). For Study Nos. (b) (4) 303-043 and (b) (4) 303-044, AUC was multiplied by a factor of 2 to account for the difference in dosing regimen (every 2 weeks) compared to UX023-CL303 (every 4 weeks) for adults. The AUC was not adjusted for Study No. (b) (4) 303-020 since the pediatric human and juvenile monkey dose regimens were both every 2 weeks.

^dMonkey male (C_{max}=2,240 ng/mL; AUC=752,000 ng×h/mL, at 20th dose)

^eMonkey female (C_{max}=17,100 ng/mL; AUC=5,820,000 ng×h/mL, at 20th dose)

^fAverage of mean values in monkey male and female were considered (for female: C_{max}=12,500 ng/mL; AUC=1,830,000 ng×h/mL and for male: 12,900 ng/mL; AUC=1,910,000 ng×h/mL, at 20th dose)

^g1 to < 5 years old pediatric patients

^h5 to < 12 years old pediatric patients

ⁱPregnant dam on GD132 at 9th dose (C_{max}=15,400 ng/mL; AUC=5,080,000 ng×h/mL, at 0.3 mg/kg; C_{max}=135,000 ng/mL; AUC=42,600,000 ng×h/mL, at 3 mg/kg; C_{max}=1,220,000 ng/mL; AUC=370,000,000 ng×h/mL, at 30 mg/kg)

NOTES:

a) For Study (b) (4) 303-043, the NOAEL for shortened gestation period was 0.3 mg/kg (IV), and the NOAEL for abortions/embryofetal deaths and placental mineralization was 3 mg/kg (IV).

b) For Studies (b) (4) 303-044 and (b) (4) 303-043, AUC (AUC_{last}) was multiplied by a factor of 2 to account for the difference in dosing regimen between the animal studies (Q2W) and adult human Study UX023-CL303 (Q4W).

5.6. Nonclinical Safety Issues

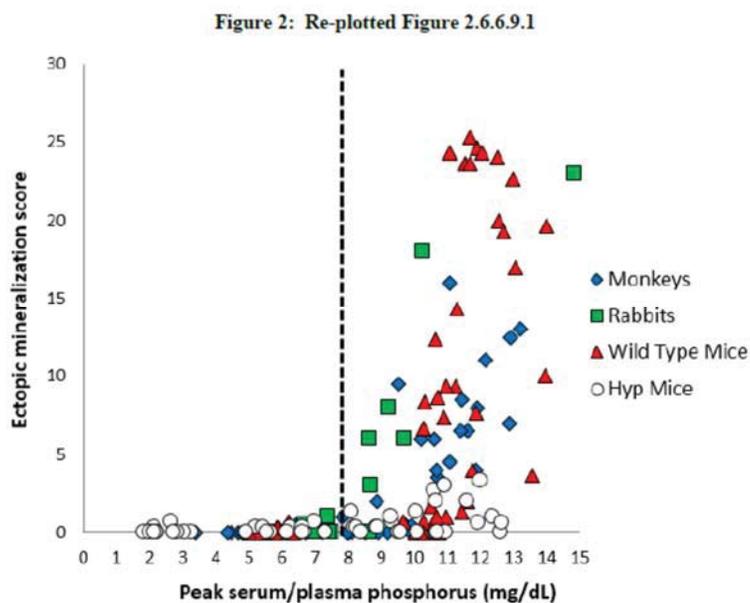
Ectopic Mineralization

NOAELs and NOAEL-based AUC multiples were very low (≤1x), due to the finding of ectopic mineralization at the LOAEL. To explore this finding in more depth, the applicant determined

the correlations between serum phosphorus and “mineralization score” for studies in rabbits, monkeys and WT/Hyp mice. The mineralization score was defined for each animal as the sum of severities, using a 4-point scale, of all organ/tissue mineralization findings. Paired organs were averaged except for the mouse study. The correlation was also determined for serum Ca and 1,25(OH)2VitD (not shown). Although studies in different species were of different durations, the correlations indicated that mineralization only occurred when peak serum phosphorus exceeded a threshold of approx. 8 mg/dL in monkeys and rabbits and 10 mg/dL in mice, and that above the threshold mineralization was positively correlated to peak serum phosphorus (Figure 11 below).

Notably, the correlation between peak serum phosphorus and mineralization was different for WT and Hyp mice, with Hyp mice exhibiting much less mineralization at particular peak IP values. Comparison of ectopic mineralization scores in adult and juvenile monkeys showed a slightly lower score in juveniles vs adults (not shown), but the differences between adult and juvenile monkeys with regard to burosumab PK and number of tissues contributing to the mineralization make this finding difficult to interpret. The correlations between peak serum Ca or 1,25(OH)2VitD and mineralization score appeared to be weaker than those for peak serum phosphorus, for monkeys and rabbits.

Figure 11 Ectopic Mineralization Score

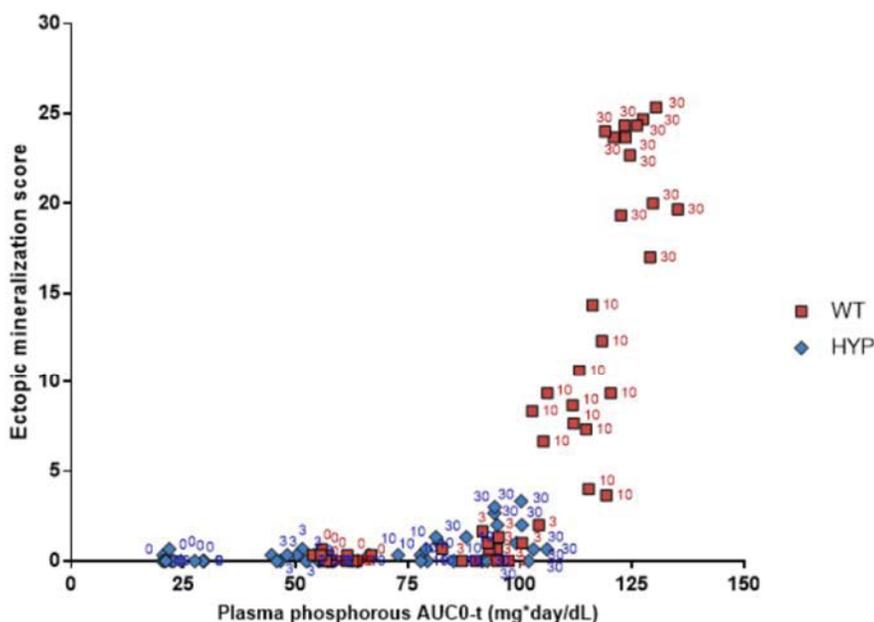


A better correlation existed between $AUC(IP)_{[0-14 \text{ days}]}$ and mineralization score in mice (Figure 12 below). This correlation was also very similar for WT and Hyp mice. Apparently, the difference in mineralization score between WT and Hyp mice (Figure 11, above) was based on a

shorter duration of the serum phosphorus increase in Hyp animals. Figure 12 (below) shows that the mineralization score was similar in Hyp mice at 30 mg/kg as in WT mice at approx. 3 mg/kg.

Figure 12 Inorganic Phosphorus AUC and Mineralization Score

Figure 1: Comparison of Plasma Inorganic Phosphorus AUC with Ectopic Mineralization in Wild Type and Hyp Mice given a Murine Anti-FGF23 Antibody



Ectopic mineralization score represents a summation of all mineralization findings (Day 14) in an individual animal. Severity was scored as 0 (no abnormal change), 1 (very slight), 2 (slight), 3 (moderate), and 4 (marked). For each tissue except specific lung lobes, an average of 3 slides was used to represent a severity score for a given tissue. For anterior, middle and posterior lung, only 1 slide was read and that severity score was included in the total summation of mineralization scores for an individual animal. Labels next to data points indicate the dose level, in mg/kg, associated with the wild type or Hyp mouse represented. Plasma phosphorus concentrations and histopathology raw data were obtained from the main group of animals in Study (b) (4) 303-084 that received repeated doses of a murine anti-FGF23 antibody.

The applicant noted that normal animals are overly sensitive to mineralization since they have normal phosphorus and FGF23 metabolism/levels and their serum phosphorus increases to supraphysiological levels upon treatment with burosumab. Thus, from the perspective of the hypophosphatemic state, the mineralization can be considered an exaggerated pharmacological response. Support for this conclusion was derived from the mouse study showing less mineralization in Hyp vs WT mice, i.e. decreased sensitivity under hypophosphatemic conditions. The applicant concluded that the mineralization was likely caused by the elevated serum phosphorus levels. It was also considered that the animal mineralization finding has limited clinical relevance, since XLH patients would be much less sensitive to this type of toxicity. Accordingly, the low NOAEL multiples that are based on this adverse finding were

considered of limited value. The applicant concluded that the risk for mineralization in XLH patients is managed by controlling serum phosphorus and calcium to an age-matched normal range.

This reviewer agrees with the applicant, that the ectopic mineralization was related to the elevations in serum phosphorus concentrations. The variability in the correlations was probably, in part, due to the choice of peak serum phosphorus as an independent variable. The improved correlation in mice when using AUC-IP as an independent variable confirmed that the duration of serum phosphorus increase was also an important factor and that AUC- phosphorus is a better predictor than peak phosphorus for mineralization.

While the applicant concluded that based on the correlations serum phosphorus caused the ectopic mineralization, other factors, e.g. serum and/or urine Ca or 1,25(OH)₂VitD, most likely also contributed. FGF23-null mice display similar features as burosumab-treated normal animals, e.g. hyperphosphatemia, hypercalcemia, hypervitaminosisD, osteopenia, and soft tissue calcifications in kidney and heart (Martin et al, 2012). Vitamin D receptor (VDR) ablation or inhibition of (1,25)VitD-hydroxylase rescues this phenotype. Therefore, the calcifications in this model are probably due to combined increases in serum Ca and/or phosphorus and perhaps local effects of VitD. These may also be the main factors involved in the ectopic mineralization caused by burosumab. There is also a possibility of a direct effect of low FGF23 on cardiovascular mineralization in burosumab-treated animals based on a claimed calci-protective role of FGF23 in the cardiovascular system (Lim et al, 2012). However, this is contradicted by the rescue of the FGF23 null mice abnormalities by Vitamin D blockade.

This reviewer agrees with applicant that normal animals are more sensitive to ectopic mineralization than XLH patients or hypophosphatemic animals. In the mouse study, the NOAEL for an increase in mineralization was similar in WT and Hyp mice (< 3 mg/kg), as mineralization was increased in both types at the lowest dose of 3 mg/kg. However, the incidence and/or severity of the mineralization was less in Hyp than WT mice at all doses, and the similar mineralization in 30 mg/kg Hyp and 3 mg/kg WT mice suggests that Hyp mice are approx. 10x less sensitive to mineralization than WT animals, assuming PK is similar in the two genotypes. This underscores that not only the NOAEL but also the extent of the effect at the LOAEL (and above) is important for data interpretation.

Treatment of XLH patients is aimed at increasing their serum phosphorus levels to the normal range. Since serum phosphorus appears to be a reasonable marker for mineralization based on the established correlations, the concern about ectopic mineralization for XLH patients (e.g. in kidney or heart) is small. However, as suggested by the Hyp mouse study, any increase in serum phosphorus and 1,25(OH)₂VitD and possibly Ca, increases the risk for mineralization to a small extent also in the low to normal range of serum phosphorus concentrations. This increase is not easily resolved in the correlation graphs but is demonstrated by the dose-related increase in

group incidences in the mouse study. The risk for ectopic mineralization may be minimized by adequately controlling serum phosphorus and Ca in XLH patients to the low-normal range.

ADCC issue

The positive result of the Antibody-Dependent Cellular Cytotoxicity (ADCC) assay in HEK-18 cells suggested the potential for immune cell mediated cytotoxicity, i.e., "Type II hypersensitivity". The toxicity is supposedly mediated by binding of the C-terminal part of FGF23 in the burosumab-FGF23 complex to α Klotho or the α Klotho-FGFR1 interface on the cell surface. Since α Klotho is the obligatory coreceptor for FGF23 and confers tissue specificity to the effects of FGF23, this toxicity would manifest in FGF23 target cells. However, cells containing only α Klotho could also be affected. Kidney is the main organ expressing FGFR and α Klotho, but both entities are also present in parathyroid, brain (choroid plexus) and probably cardiovascular tissue. Apart from kidney and artery, expression of transmembranous α Klotho has been demonstrated in various human tissues including epithelial, endocrine and neuronal human cells/tissues (Lim et al, 2015). Histologically, ADCC-like toxicity would be evident as cell necrosis and inflammation, while functional consequences of ADCC toxicity could also occur. Clinical examples of Type II hypersensitivity include autoimmune diseases such as Graves' disease, myasthenia gravis, and rheumatic heart disease.

The applicant argued that the risk/concern for ADCC-like toxicity is low due to: (1) tissue specificity, (2) overprediction of toxicity by the assay since it was conducted in Klotho-over-expressing cells, (3) animal toxicities consisting of mineralization and sequelae rather than antibody-induced injury. This reviewer does not agree that toxicity would be limited to FGF23/Klotho target tissues, since Klotho-expressing tissues not involved in FGF23 phosphate transport signaling could also be affected. The consequence of Klotho-overexpression in the HEK-18 cells is unclear. Additionally, the maximum burosumab concentration of 100 ng/mL in the assay was smaller than in vivo serum concentrations (Human C_{max} = approx. 11000 ng/mL, and AUC(0-30days)/30days= approx. 7000 ng/mL). However, the serum distribution of burosumab suggests that local tissue concentrations of burosumab may be smaller than C_{max}.

In the 14- and 40-week monkey toxicity studies, microscopic kidney toxicity other than tubule/Henle loop mineralization included tubule degeneration/necrosis, tubule regeneration, edema, increase in multinucleate tubule epithelial cells, tubule dilation, interstitial fibrosis, and inflammatory cell infiltration. These lesions were observed at 3 and 30 mg/kg, and only in animals in which tubule mineralization was present, with one exception (one 3 mg/kg juvenile monkey that died of infection, with kidney fibrosis but no mineralization). The severity of the tubule mineralization was minimal to moderate, and for the other renal findings it was generally minimal to slight, although moderate fibrosis was observed in one 30 mg/kg male monkey with slight mineralization in the 40-week study. The applicant considered that these renal lesions were secondary to renal mineralization. Other renal effects, e.g. increased urine protein or BUN, were also considered related to renal mineralization. While the coincidence suggests relatedness, there is some uncertainty as to whether ADCC could have contributed in

part to the renal injury. A correlation between the severity of the mineralization and that of the other renal lesions to clarify this issue could not clearly be established.

In rat and dog studies conducted with the Vitamin D analog paricalcitol (Zemplar; NDA 20819), kidney, heart and gastrointestinal mineralization was associated with drug-induced hypercalcemia. The kidney mineralization was accompanied by tubule degeneration and regeneration, tubule dilatation, fibrosis and inflammation, similar to what was observed in burosumab-treated rabbits and monkeys, and these lesions were considered secondary to mineralization. The animal findings with paricalcitol support the idea that the renal lesions are secondary events occurring in the context of hypercalcemia and/or hyperphosphatemia and are not independent drug effects.

Other potential FGF23 target tissues (parathyroid, choroid plexus) showed mineralization in burosumab-treated monkeys in 14- and/or 40-week studies. Parathyroid decreased/alterd cytoplasm and parathyroid atrophy were also observed at 3 mg/kg in the 13-week rabbit study and at 30 mg/kg in the 14-week monkey study. These parathyroid changes and the few other microscopic findings in monkeys in the spleen (lymphocyte, decreased germinal center) and trachea (basophilia, metaplasia) do not appear to represent ADCC-like cytotoxicity. In WT and Hyp mice, there was kidney, lung and/or heart/aorta mineralization, but no other microscopic finding.

The utility of a longer than 14-day study in WT and Hyp mice to provide further information on potential ADCC-related toxicity was considered, since mineralization and sequelae would be expected to be more extensive in WT than Hyp mice, while ADCC toxicity would not. However, such a study would need to be conducted with a murine anti-FGF23 antibody. Considering the available data and the likely species-specificity and antibody-dependence of an ADCC type effect, the usefulness of an additional mouse study appears small.

In conclusion, the available data suggest that burosumab does not appear to evoke significant ADCC toxicity in rabbits or monkeys. However, this type of hypersensitivity is likely to be species-specific and it cannot be excluded that it could occur in humans. This issue should be addressed independently in the clinical safety review.

5.7. Nonclinical Labeling

Sponsor's proposed PI (Submitted with BLA, August 17, 2017)

8. Use in Specific Populations

8.1 Pregnancy

Risk Summary

(b) (4)

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

(b) (4)

Burosumab was detected in serum from fetuses indicating that burosumab was transported across the placenta

(b) (4)

burosumab did not affect pre- and postnatal growth including survivability of the offspring.

Reviewer's comments (Section 8.1):

- *DMPH and Pharm/Tox review teams made extensive edits to Section 8.1 to make it more comprehensible and more clear for prescribers.*
- *This included adding a summary of the monkey ePPND study and general clinical recommendations to the Risk Summary, and providing details of the monkey study in the Animal Data section.*
- *The finding of an increase in fetal loss at the 30 mg/kg high dose in the monkey study was added to the Risk Summary and the Animal Data.*

8.2 Lactation

Risk Summary

There is no information regarding the presence of burosumab in human milk, the effects on the breastfed infant, or the effects on milk production. (b) (4)

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for CRYSVITA and any potential adverse effects on the breastfed infant from CRYSVITA or from the underlying maternal condition.

Reviewer's comments (Section 8.2):

- *Section was edited by DPMH.*

8.3 Females and Males of Reproductive Potential

(b) (4)

Reviewer's comments (Section 8.3):

- *This section was removed per DPMH's recommendation. The Pharm/Tox review team agreed. Rationale included lack of specific fertility studies.*
- *Information on reproductive organ effects in non-XLH animal studies did not suggest any concerns and is mentioned in Section 13.1.*

12.1 Mechanism of Action

X-linked hypophosphatemia is caused by excess fibroblast growth factor 23 (FGF23). Burosumab binds to and inhibits the biological activity of FGF23 restoring renal tubular reabsorption of phosphate and increases serum concentration of 1,25 dihydroxy-vitamin D.

Reviewer's comments (Section 12.1):

- *Text was edited for clarity.*

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of burosumab has not been evaluated in long term studies.

Studies have not been performed to evaluate the mutagenic potential of burosumab.

No specific fertility studies in animals have been performed to evaluate the effect of burosumab.

(b) (4)

Reviewer's comments (Section 13.1):

- *Minor edits were made in this section in order to present the animal data clearly and accurately.*

13.2 Animal Toxicology and/or Pharmacology

(b) (4)

Reviewer's comments (Section 13.2):

- *This section was extensively re-organized and edited for clarity and completeness.*

Prescribing information related to these nonclinical sections incorporated recommendations from DPMH and were conveyed to the applicant.

6. Clinical Pharmacology

6.1. Executive Summary

Burosumab is a human IgG1 monoclonal antibody that binds to human fibroblast growth factor 23 (FGF23).

- **Proposed indication:** For the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.
- **Proposed dosing regimen:** Burosumab is administered by subcutaneous (SC) injection. Dosing of burosumab is body weight based and titrated to achieve normal serum phosphorus level. The proposed dose for pediatric subjects 1 to <18 years of age is 0.8 mg/kg Q2W as starting dose with dose titration up to 2 mg/kg (and with a maximum dose of 90 mg). The proposed dose for adults is 1 mg/kg Q4W as starting dose with dose titration up to a maximum dose of 90 mg.
- **Proposed dosage forms:** 10 mg/mL, 20 mg/mL, and 30 mg/mL solution for injection in a single-dose vial

The applicant has evaluated the efficacy and safety of burosumab in XLH patients 1 to 4 years of age (Study UX023-CL205), XLH patients 5 to 12 years of age (Study UX023-CL201), and adult XLH patients (Study UX023-CL303). The applicant has not conducted clinical trials to investigate efficacy and safety of burosumab in adolescent XLH patients 13 to <18 years of age. The applicant additionally submitted the results of Phase 1/2 trials in subjects with XLH to support clinical pharmacology information of burosumab.

The key review findings are summarized in **Table 17**.

Table 17 Summary of clinical pharmacology review

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	<ul style="list-style-type: none">• The efficacy of burosumab for the treatment of XLH is established in XLH patients 1 to 4 years of age (Study UX023-CL205), XLH patients 5 to 12 years of age (Study UX023-CL201), and adult XLH patients (Study UX023-CL303).• Serum phosphorus level is the primary PD endpoint in the clinical development of burosumab for XLH. The effectiveness of burosumab in increasing serum phosphorus

Review Issue	Recommendations and Comments
	<p>levels has been established across clinical studies in subjects with XLH.</p> <ul style="list-style-type: none"> Exposure-response analysis for efficacy provide supportive evidence for efficacy.
General dosing instructions	<ul style="list-style-type: none"> The proposed burosumab dosing regimens of 0.8 mg/kg Q2W with dose titration up to 2.0 mg/kg (a maximum dose of 90 mg) for pediatric subjects 1 to <18 years of age and 1 mg/kg Q4W with dose titration up to a maximum dose of 90 mg for adults to achieve normal serum phosphorus levels are acceptable.
Dosing in patient subgroups (intrinsic factors and extrinsic factors)	<ul style="list-style-type: none"> The recommended burosumab dose is body weight based and titrated to achieve a normal serum phosphorus level. No further dose individualization is recommended based on other intrinsic or extrinsic factors.
Drug interactions	<ul style="list-style-type: none"> Drug interaction studies have not been conducted with burosumab.
Immunogenicity	<ul style="list-style-type: none"> No subjects were found positive for treatment-emergent anti-drug antibodies (ADA) in burosumab XLH clinical studies due to the limitation of the immunogenicity assays in the BLA. See related outstanding issues and PMC/PMR recommendations.
Bridge between the to-be-marketed and clinical trial formulations	<ul style="list-style-type: none"> The to-be-marketed 10 mg/mL, 20 mg/mL, and 30 mg/mL solution for injection have the same drug product formulation with different drug concentration strength. The 10 mg/mL and 30 mg/mL solution were used in clinical trials; therefore, there is no need to bridge the to-be-marketed formulation to the clinical trial formulation for these two strength. The overall biopharmaceutics data also supported approval of the 20 mg/mL strength.

An OCP office level briefing was held on January 17, 2018.

Recommendations

From a Clinical Pharmacology’s standpoint, the BLA is acceptable to support the approval of CRYSTIVA (burosumab) for the treatment of X-linked hypophosphatemia (XLH) in adult and

pediatric patients 1 year of age and older, provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the labeling.

Post-Marketing Requirements and Commitments (PMC/PMR)

- To conduct a study to reanalyze banked immunogenicity serum samples from XLH clinical trials including Study UX023-CL205, Study UX023-CL201, and Study UX023-CL303 to determine the presence of anti-drug antibodies (ADA) using a validated ADA assay with improved drug tolerance. Characterize the neutralizing activity of ADA for samples tested positive for ADA. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy and safety in adult and pediatric subjects with XLH based on the ADA data generated with the newly validated assay.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of action and pharmacodynamics

- *Mechanism of action (MOA)*: Burosumab is a recombinant human IgG1 monoclonal antibody that binds to fibroblast growth factor 23 (FGF23). By inhibiting the biological activity of FGF23, burosumab restores renal tubular reabsorption of phosphate and increases serum concentration of 1, 25 dihydroxy-vitamin D.
- *Effect on serum FGF23 levels*: Elevations in serum total FGF23 levels were observed after initiation of burosumab treatment.
- *Effect on serum phosphate levels*: Following SC administration of burosumab in XLH patients, serum phosphate levels increased in a burosumab concentration-dependent manner. Higher burosumab concentrations were associated with greater increase of serum phosphate levels. The increase in serum phosphate was reversible and returned to near baseline with elimination of systemic burosumab.

Pharmacokinetics of busosumab

The PK of burosumab was described by a one-compartment PK model with first order absorption and first-order elimination following subcutaneous injection. Burosumab exhibited linear pharmacokinetics following SC injections within the dose range of 0.1 to 1 mg/kg. The

apparent clearance was estimated to be 0.290 L/day for a subject of 70 kg of body weight and the estimated half-life of burosumab was approximately 19 days. Clearance of burosumab increases when body weight increases. Age was found not to significantly influence burosumab PK.

Drug interactions

Drug interaction studies have not been conducted with burosumab. No clinically relevant drug-drug interactions were identified that require further assessment (See Section 6.3.2.).

Immunogenicity

No subjects were found positive for treatment-emergent anti-drug antibodies (ADA) in burosumab XLH clinical studies. This may have been a result of the limitation of the immunogenicity assays. As a result, it is not feasible to evaluate the impact of immunogenicity on PK, efficacy or safety of burosumab in XLH patients.

6.2.2. General Dosing and Therapeutic Individualization

General dosing

The proposed burosumab dosing regimens of 0.8 mg/kg Q2W with dose titration up to 2.0 mg/kg (a maximum dose of 90 mg) for pediatric subjects 1 to <18 years of age and 1 mg/kg Q4W with dose titration up to a maximum dose of 90 mg for adults to achieve normal serum phosphorus levels are acceptable. The proposed dosing regimen is supported by the efficacy results from Study UX023-CL205 (1 to 4 years of age), Study UX023-CL201 (5 to 12 years of age), and Study UX023-CL303 (adults). The proposed dosing regimen in adolescent subjects (13 to <18 years of age) is supported by population PK and exposure-response analysis results.

Therapeutic individualization

Population PK analysis identified body weight as a significant covariate on burosumab PK. However, because dosing of burosumab is based on body weight and individually titrated to achieve normal serum phosphorus levels, we do not recommend further dose individualization based on other intrinsic or extrinsic factors. Body weight did not show an impact on efficacy in burosumab XLH adult and pediatric clinical trials.

Outstanding Issues

There are no outstanding issues that would preclude the approval of burosumab from a Clinical Pharmacology's perspective.

Current electrochemiluminescent (ECL) immunogenicity assay for detection of anti-drug antibodies (ADA) used in burosumab XLH clinical studies had drug tolerance level of 3.75 mcg/mL burosumab (determined at a high ADA concentration of 2000 ng/mL). This drug

tolerance level is lower than the mean steady-state drug concentrations observed in burosumab XLH clinical studies indicating the limitation of the current assay to detect ADA in the presence of burosumab.

No subjects who were ADA negative at baseline were tested ADA positive following burosumab treatment. This likely is attributed to the limitation of the assay. Therefore, the ADA incidence and its clinical impact for burosumab in XLH subjects could not be assessed with the current data.

See PMC/PMR recommendations to address the assay issue through development of an optimal assay.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of the general clinical pharmacology, pharmacokinetics, and immunogenicity of burosumab is provided in **Table 18**.

Table 18 Summary of clinical pharmacology, pharmacokinetics and immunogenicity of burosumab

Pharmacology	
Mechanism of Action	XLH is caused by excess fibroblast growth factor (FGF23). Burosumab binds and inhibits FGF23. By inhibiting FGF23, burosumab restores renal tubular reabsorption of phosphate and increases serum concentration of 1, 25 dihydroxy-vitamin D.
Pharmacodynamics	<p>1. Phosphorus</p> <p><i>Study UX023-CL303 (adult subjects)</i></p> <p>In the burosumab treatment group (n = 68, Q4W), mean (\pmSD) serum phosphorus level at baseline was 2.03 \pm0.30 mg/dL, mean across the mid-point of the dose intervals to Week 24 was 3.24 \pm0.53 mg/dL, and mean across the end of the dose intervals to Week 24 was 2.72 \pm0.45 mg/dL. In the placebo group (n = 66, Q4W), mean (\pmSD) serum phosphorus level at baseline was 1.92 \pm0.32 mg/dL, mean across the mid-point of the dose intervals to Week 24 was 2.08 \pm0.30 mg/dL, and mean across the end of the dose intervals to Week 24 was 2.05 \pm0.30 mg/dL.</p>

	<p>In this study, the normal serum phosphorus range in adults was defined to be 2.5-4.5 mg/dL. A total of 94.1% (64/68) of subjects in the burosumab group achieved a mean serum phosphorus concentration above the lower limit of normal (LLN) across the midpoints of the dose intervals through Week 24, compared with 7.6% (5/66) of subjects in the placebo group. Through Week 24, nine subjects in the burosumab group had high serum phosphorus (> 4.5 mg/dL) at least once; five of the nine subjects required protocol-specified dose reduction(s).</p> <p><i>Study UX023-CL201 (pediatric subjects 5-12 years of age)</i></p> <p>In the Q2W group (n=26), mean (\pmSD) serum phosphorus levels increased over time from 2.38 \pm0.41 mg/dL at Baseline, to 3.30 \pm0.40 mg/dL at Week 40, to 3.35 \pm0.45 mg/dL at Week 64. In the Q4W group (n=26), mean (\pmSD) serum phosphorus levels increased from 2.28 \pm0.30 mg/dL at Baseline, to 3.38 \pm0.40 mg/dL at Week 38 (mid-point of the dosing interval), to 3.50 \pm0.37 mg/dL at Week 62 (mid-point of the dosing interval).</p> <p>In this study, the normal serum phosphorus range in pediatric subjects 5-12 years of age was defined to be 3.2-6.1 mg/dL. Overall, 94.2% (49/52) subjects ever reached the normal range and no subject had serum phosphorus levels above upper limit of the normal range.</p> <p><i>Study UX023-CL205 (pediatric subjects 1-4 years of age)</i></p> <p>All subjects (n=13) received burosumab every other week. Mean (\pmSD) serum phosphorus levels increased over time from 2.51 \pm0.28 mg/dL at Baseline, to 3.70 \pm0.48 mg/dL at Week 1, to 3.53 \pm0.65 mg/dL at Week 15, and to 3.35 at \pmWeek 20.</p> <p>In this study, the normal serum phosphorus range in pediatric subjects 1-4 years of age was defined to be 3.2-6.1 mg/dL. Overall, 92.3% (12/13) subjects ever reached the normal range and no subject had serum phosphorus levels above upper limit of the normal range.</p> <p>2. Total FGF23</p> <p>Elevations in serum total FGF23 levels were observed after initiation of burosumab treatment.</p>
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	<p>In Study UX023-CL303 (adult subjects), increased FGF23 levels were observed through Week 24 in the burosumab group. Mean (\pmSE) serum total FGF23 increased from 158.69 \pm40.97 pg/mL at baseline to 217.64 \pm14.02 ng/mL at Week 24.</p> <p>In Study UX023-CL201 (pediatric subjects 5-12 years of age), mean (\pmSD) serum total FGF23 concentrations in all the treated subjects (n=52) at Baseline were 0.16 (\pm0.10) ng/mL and ranged from 0.03 to 0.45 ng/mL. Mean (\pmSD) total FGF23 concentrations increased following burosumab treatment to 175 \pm119 ng/mL at Week 8, to 253 \pm152 ng/mL at Week 16, to 429 \pm209 ng/mL at Week 38, and to 470 \pm253 ng/mL at Week 64. Mean total FGF23 concentrations were greater in the Q2W group (n=26) than in the Q4W group (n=26) at each postbaseline time point up to Week 64, indicating a burosumab dose-dependent manner in elevated FGF23 concentrations.</p>
<p>General Information</p>	
<p>Bioanalysis</p>	<p>1. PK assay</p> <p>Two different assay systems were used for measuring serum burosumab levels: an enzyme-linked immunosorbent assay (ELISA) and an electrochemiluminescent (ECL) based sandwich assays. Both the ELISA and the ECL assays have been validated by the applicant. The two PK assays used an identical pair of specific monoclonal antibodies with different conjugates for capture and detection of burosumab.</p> <p>2. Serum Phosphorus assay</p> <p>The serum phosphorus assay measures inorganic phosphate in serum and the assay procedure involves the formation of phosphomolybdate. Phosphomolybdate is measured at 340 nm and is directly proportional to the amount of inorganic phosphate in serum sample.</p> <p>3. Total FGF23 assay</p> <p>An electrochemiluminescent (ECL) assay based on Meso-Scale Discovery (MSD) platform was developed to measure the total FGF23 (free and burosumab bound) in human serum. Antibodies used in ECL are specific for different epitopes on the FGF23 molecule and do not compete with burosumab.</p>

PK model	The PK of burosumab was described by a one-compartment PK model with first order absorption and first-order elimination following subcutaneous injection.
Drug concentrations at steady state	<p>In Study UX023-CL303 (adult subjects), mean \pmSD steady state peak (Week 20) and trough (Week 24) were 10.09 \pm4.28 mcg/mL and 5.83 \pm3.43 mcg/ml, respectively.</p> <p>In Study UX023-CL201 (pediatric subjects 5-12 yrs of age), mean \pmSD serum burosumab concentration at Week 64 (trough) was 15.85 \pm9.39 mcg/mL in the Q2W group and 8.53 \pm3.97 mcg/mL in the Q4W group.</p> <p>In Study UX023-CL205 (pediatric subjects 1-4 yrs of age), the mean \pmSD serum burosumab concentration was 11.16 \pm4.62 mcg/mL at Week 12 (trough).</p>
Dose Linearity	The mean values for Cmax and AUC increased in a dose-proportional manner within the dose range of 0.1 to 1.0 mg/kg.
Body weight	Body weight was a significant covariant on the clearance (CL/F) and volume of distribution (V/F) of burosumab. Subjects with higher body weight were associated with higher values in clearance and volume of distribution.
Hepatic and Renal Impairment	No formal studies were conducted to assess the effect of hepatic and renal impairment on the PK of burosumab.
ADME	
Absorption	Following single SC administration of burosumab, the mean Tmax values across all dose levels (0.1 to 1.0 mg/kg) ranged from 8 to 11 days. Following multiple SC administrations, based on the estimated typical burosumab elimination $t_{1/2}$ of 19 days, the time to reach 90% of steady-state plateau exposure is approximately 67 days and the systemic accumulation is estimated to be 2.5-fold and 1.6-fold for once every 2 weeks and once every 4 weeks dosing regimens, respectively.
Distribution	The estimated volume of distribution at steady-state using non-compartment analysis was 43.6-57.2 mL/kg following a single IV administration of 0.01 to 0.3 mg/kg. The apparent volume of distribution of burosumab is estimated to be 8 L for a subject of 70 kg of body weight based on a population PK analysis.

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(burosumab - twza)

<p>Elimination</p>	<p>Mean systemic clearance (CL/F) of burosumab was estimated to be 0.140-0.206 mL/hr/kg, following a single IV administration of 0.01 to 0.3 mg/kg. The population PK analysis showed that the apparent clearance was estimated to be 0.290 L/day for an adult subject of 70 kg of body weight.</p> <p>Mean elimination half-life ($t_{1/2}$) of burosumab was estimated to be 13 to 19 days, following a single SC administration of 0.1 to 1.0 mg/kg. Mean elimination half-life ($t_{1/2}$) of burosumab was estimated to be 8 to 12 days, following a single IV administration of 0.01 to 0.3 mg/kg. The population PK analysis estimated half-life of burosumab was approximately 19 days.</p>
<p>- Metabolism</p>	<p>The exact pathway through which burosumab is metabolized has not been characterized. As a human monoclonal antibody, burosumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.</p>
<p>- Excretion</p>	<p>The renal excretion of burosumab has not been studied. Burosumab is a humanized monoclonal antibody of the IgG1 subclass and has a molecular weight of approximately 147 kDa; therefore, intact burosumab antibodies are unlikely to be filtered by kidney or excreted in urine.</p>
<p>Immunogenicity</p>	
<p>ADA assay</p>	<p>The current ADA assay had burosumab drug tolerance level of 3.75 mcg/mL (determined at a very high ADA concentration of 2000 ng/mL). This drug tolerance level is lower than majority of serum burosumab concentrations measured in burosumab XLH clinical studies.</p>
<p>Incidences</p>	<p>In pediatric studies, 4 out of 65 subjects (6.2%) were tested positive for ADA at baseline. In adult studies, 18 out of 175 subjects (10.2%) were tested positive for ADA at baseline.</p> <p>No subjects who were negative for ADA at baseline were tested positive for ADA following burosumab treatment likely due to the limitation of the ADA assay.</p>
<p>Impact on PK, Efficacy and Safety</p>	<p>It is not feasible to evaluate the impact of immunogenicity on burosumab PK, efficacy or safety because no subjects were found to have treatment-emergent ADA using the current assay.</p>

6.3.2. Clinical Pharmacology Review Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

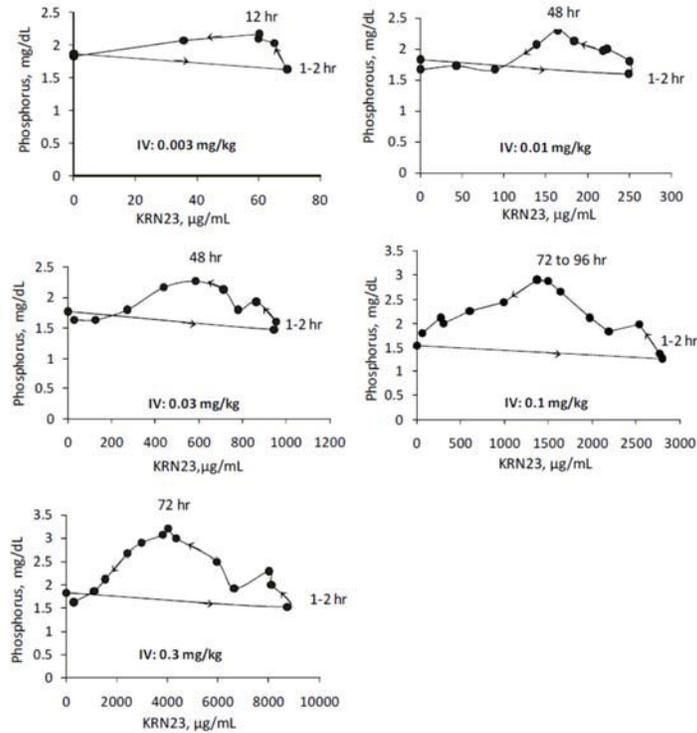
Yes. Serum phosphorus level is the primary PD endpoint in the clinical development of burosumab for patients with XLH. The effectiveness of burosumab in increasing serum phosphorus levels has been established across clinical studies in subjects with XLH. The exposure-response for efficacy (i.e., increase in serum phosphorus levels) also provides supportive evidence of effectiveness.

Study KRN23-US-02

Study KRN23-US-02 was a Phase 1, double-blind, randomized, placebo-controlled, single-dose escalation study. This study characterized the PK/PD profile of burosumab (KRN 23) following a single IV or SC administration in adult XLH subjects. The dose levels in the burosumab IV treatment arm were 0.003, 0.01, 0.03, 0.1, and 0.3 mg/kg. The dose levels evaluated in the burosumab SC treatment arm were 0.1, 0.3, 0.6, and 1.0 mg/kg. A total of 29 patients had valid burosumab serum concentration data and were included in the PK analysis.

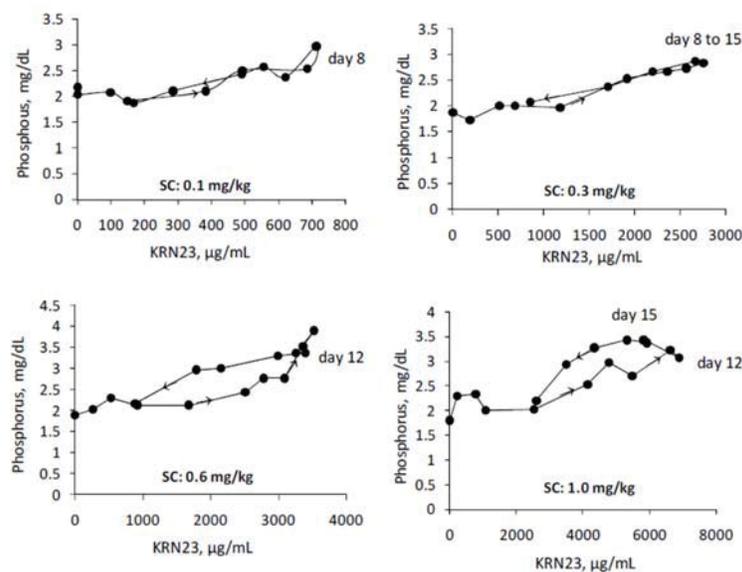
Mean serum phosphorus concentration versus mean serum burosumab (hereafter also referred to as KRN23) concentration profiles following single IV and SC dose administration are shown in **Figure 13** and **Figure 14**, respectively. The increase in serum phosphorus levels was delayed as KRN23 concentration increased following IV administration of KRN23. Following SC administration, serum phosphorus levels increased concurrently as KRN23 concentration increased.

Figure 13. Mean Phosphorous Concentration versus Mean KRN23 Concentration Following IV Administration in Patients with XLH



(Source of data: Figures 11.7-1 and 11.7-2 of the Clinical Study Report)

Figure 14. Mean Phosphorous Concentration versus Mean KRN23 Concentration Following SC Administration in Patients with XLH



(Source of data: Figures 11.7-1 and 11.7-2 of the Clinical Study Report)

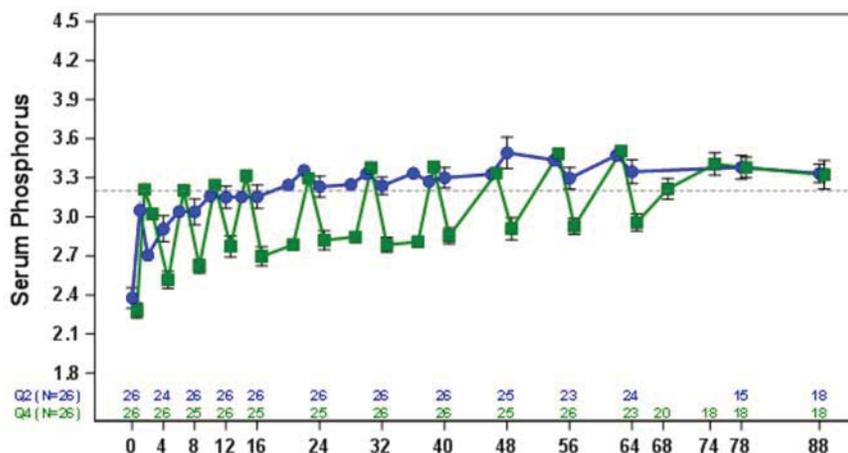
Study UX023-CL201

In Study UX023-CL201 (pediatric XLH subjects 5-12 years of age, n = 52), subjects were assigned to one of six dose cohorts, with starting doses of 0.1, 0.2, 0.3 mg/kg Q2W or 0.2, 0.4 or 0.6 mg/kg Q4W. Within each dosing frequency group, the enrollment was staggered. For individual subjects in all cohorts, dose can be increased up to 2.0 mg/kg with a maximum dose of 90 mg, as needed to achieve a pre-specified serum phosphorus range of 3.5 to 5 mg/dL. The defined serum phosphorus normal range for age is 3.2-6.1 mg/dL.

For the Q2W group, the average steady-state dose was approximately 1.0 mg/kg, with a range of 0.4-2.0 mg/kg, at weeks 40-64. For the Q4W, the average dose was higher due to the less frequent dosing. At week 64, subjects in the Q4W group switched to Q2W dosing.

Burosumab treatment substantially increase serum phosphorus levels in both the Q2W and Q4W groups as shown in **Figure 15**. In the Q2W group (n=26), mean (\pm SD) serum phosphorus levels increased over time from 2.38 ± 0.41 mg/dL at Baseline, to 3.30 ± 0.40 mg/dL at Week 40, to 3.35 ± 0.45 mg/dL at Week 64. In the Q4W group (n=26), mean (\pm SD) serum phosphorus levels increased from 2.28 ± 0.30 mg/dL at Baseline, to 3.38 ± 0.40 mg/dL at Week 38 (mid-point of the dosing interval), to 3.50 ± 0.37 mg/dL at Week 62 (mid-point of the dosing interval). Overall, 94% of subjects had a serum phosphorus level within the normal range (3.2 to 6.1 mg/dL); and no subject had serum phosphorus levels above the normal range.

Figure 15. Serum Phosphorus Levels and Change from Baseline (mg/dl) (Mean \pm SE) by Regimen



Q2 = every 2 weeks; Q4 = every 4 weeks

Note: At the beginning of the Treatment Extension Period (Week 64), all subjects received KRN23 Q2W.

Note: The dashed line indicates the lower limit of the reference range (3.2 mg/dL). SE bars are displayed only at selected visits.

(Source of data: Figure 10.2.1.1 of the Clinical Study Report)

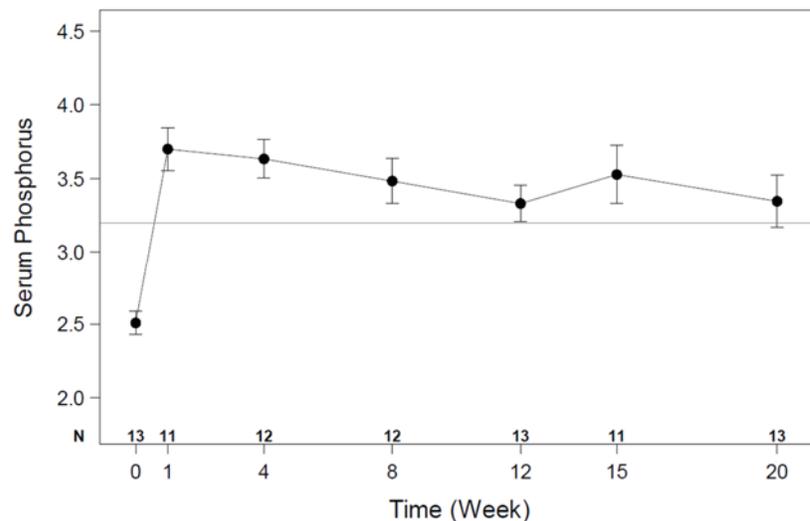
Study UX023-CL205

In Study UX023-CL205 (pediatric XLH subjects 1-4 years of age, n = 13), all subjects received KRN23 at a starting dose of 0.8 mg/kg Q2W. The dose may be increased to 1.2 mg/kg at any time if serum phosphorus increases by < 0.5 mg/dL from baseline and two consecutive measures are below LLN (unless a dose was missed). Dosing is to be held if serum phosphorus increases above ULN for age.

All subjects received 0.8 mg/kg through Week 20. At Week 22, two subjects had dose adjustments to 1.2 mg/kg based on the protocol-specified dose adjustment criteria.

At baseline, all subjects had serum phosphorus levels below normal, with a mean \pm SD of 2.51 \pm 0.28 mg/dL. Serum phosphorus levels increased rapidly with burosumab treatment and reached mean \pm SD of 3.7 \pm 0.48 mg/dL at Week 20 as shown in **Figure 16**. Overall, 92.3% (12/13) of subjects reached a serum phosphorus level within the normal range (3.2 to 6.1 mg/dL), and no subject had serum phosphorus levels above the normal range.

Figure 16. Serum Phosphorus Level (mg/dl) (Mean \pm SE) over Time in Study UX023-CL205



The dashed line indicates the lower limit of the reference range (3.2 mg/dL).
(Source of data: Figure 4.3.5.2.2 of the Clinical Study Report)

Study UX023-CL303

In Study UX023-CL303 (adult XLH subjects, n = 134), subjects were treated with burosumab or placebo Q4W. The initial dose was calculated based on baseline body weight at 1.0 mg/kg KRN23 dose level (rounded to the nearest 10 mg), up to a maximum dose of 90 mg. The dose remained fixed for the duration of the study, but can be adjusted in the event of high serum

phosphorus (>5.0 mg/dl, or two consecutive levels >4.5 mg/dl), or body weight change >20% from the baseline. The defined serum phosphorus normal range for adults is 2.5-4.5 mg/dL.

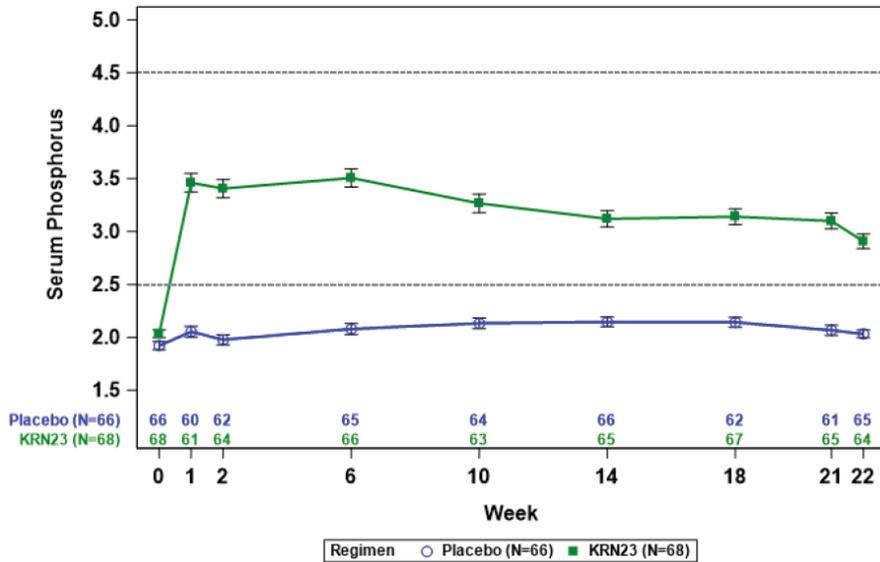
In both treatment and placebo groups, the observed median weight-based dose of blinded study drug was 1.0 mg/kg (mean: 0.99 mg/kg; range: 0.6–1.1) at Baseline Visit and remained at a dose of 1.0 mg/kg (mean: 0.97-0.98 mg/kg; range: 0.3–1.1) through all post-baseline visits through the 24 week double-blind period.

The primary efficacy endpoint for this study was the proportion of subjects achieving mean serum phosphorus concentrations above the lower limit of normal (LLN; 2.5 mg/dL [0.81 mmol/L]) at the midpoint of the dose interval, as averaged across dose cycles between baseline and Week 24.

In the burosumab treatment group (n = 68, Q4W), mean (\pm SD) serum phosphorus level at baseline was 2.03 \pm 0.30 mg/dL, mean across the mid-point of the dose intervals to Week 24 was 3.24 \pm 0.53 mg/dL, and mean across the end of the dose intervals to Week 24 was 2.72 \pm 0.45 mg/dL. In the placebo group (n = 66, Q4W), mean (\pm SD) serum phosphorus level at baseline was 1.92 \pm 0.32 mg/dL, mean across the mid-point of the dose intervals (peak) to Week 24 was 2.08 \pm 0.30 mg/dL, and mean across the end of the dose intervals (trough) to Week 24 was 2.05 \pm 0.30 mg/dL. Mean serum phosphorus concentrations across the mid-point of the dose intervals to Week 24 are shown in **Figure 17** and mean serum phosphorus concentrations across the end of the dose intervals to Week 24 are shown in **Figure 18**.

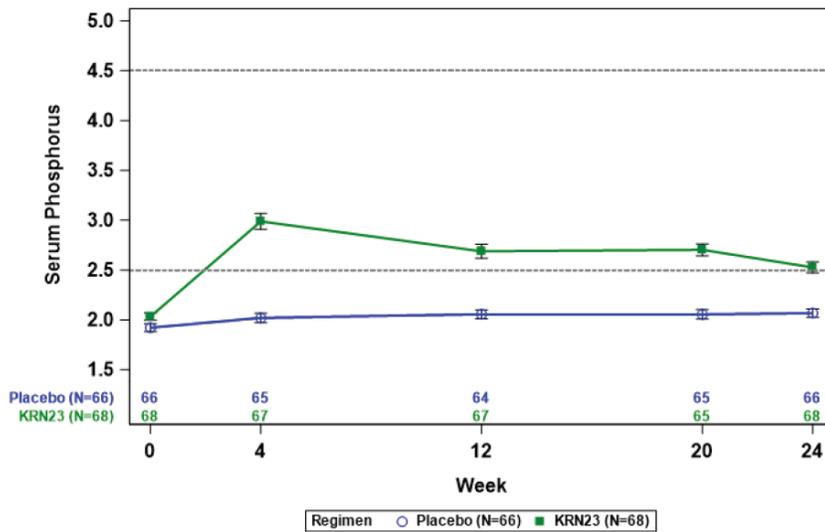
Overall, a total of 94.1% of subjects in the KRN23 group achieved a mean serum phosphorus concentration above the LLN across the midpoints of the dose intervals through Week 24, compared with 7.6% of subjects in the placebo group ($p < 0.0001$). During the 24-week double blind treatment period, nine subjects in the burosumab group had high serum phosphorus (> 4.5 mg/dL) at least once; five of the nine subjects required protocol-specified dose reduction(s).

Figure 17 Mean (\pm SE) Serum Phosphorus Concentrations (mg/dL) Across the Mid-point of the Dose Intervals to Week 24 in Study UX023-303



(Source of data: Figure 10.1.2.1 of the Clinical Study Report)

Figure 18. Mean (\pm SE) Serum Phosphorus Concentrations (mg/dL) Across the End of the Dose Intervals to Week 24 in Study UX023-303



(Source of data: Figure 10.1.2.2 of the Clinical Study Report)

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

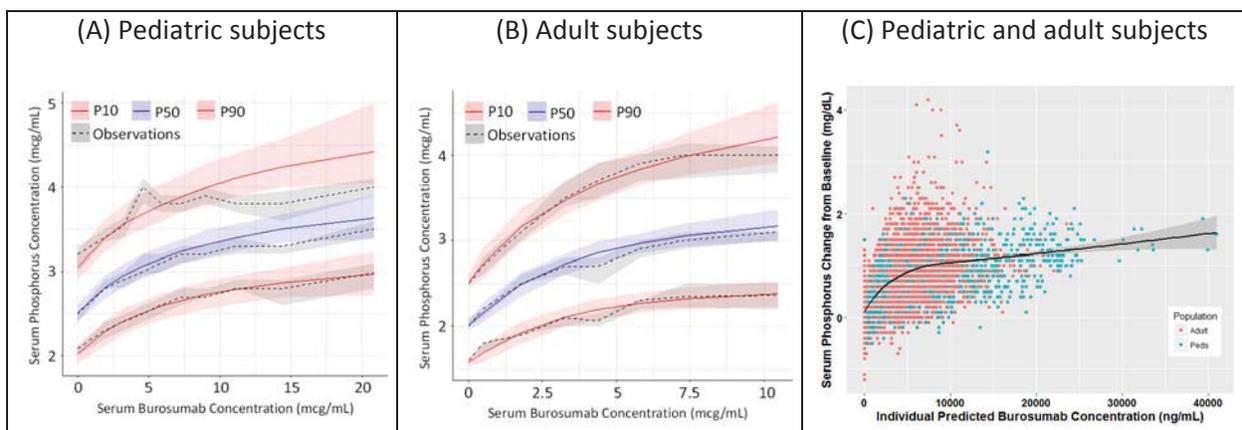
Yes, the proposed burosumab (KRN23) dosing regimens of 0.8 mg/kg Q2W as starting dose with dose titration up to 2.0 mg/kg Q2W (a maximum dose of 90 mg) for pediatric subjects 1 to <18 years of age and 1 mg/kg Q4W as starting dose with dose titration up to a maximum dose of 90 mg for adults are appropriate. Burosumab is administered by subcutaneous (SC) injection and individually titrated to achieve normal serum phosphorus level.

The proposed dose in XLH patients 1 to 4 years of age is supported by efficacy and safety results of Study UX023-CL205, the proposed dose in XLH patients 5 to 12 years of age is supported by efficacy and safety results of Study UX023-CL201, and the proposed dose in adult XLH patients is supported by efficacy and safety results of Study UX023-CL303. See Section 8 of this multi-discipline review for the related efficacy and safety data.

The applicant has not conducted clinical trials to evaluate efficacy and safety of burosumab in adolescent subjects 13 to <18 years of age. The proposed dose in adolescent subjects is supported by results of population PK/PD modeling and simulation, as described below.

The applicant developed a population PK/PD model that describes the burosumab PK and its relationship with serum phosphorus levels. The PK/PD model was based on data from five adult studies (KRN23-US-02, KRN23-INT-001, KRN23-INT002, UX023-CL203, and UX023-CL303) and two pediatric studies (UX023-CL201 and UX023-CL205). The exposure-response (E-R) relationships for serum phosphorus concentrations based on individual predicted serum burosumab concentrations in pediatric XLH patients, in adult XLH patients, and in pooled pediatric and adult XLH patients, are shown in **Figure 19** (A), (B) and (C), respectively.

Figure 19. Exposure-response relationship for serum phosphorus concentrations based on individual predicted serum burosumab concentrations in subjects with XLH



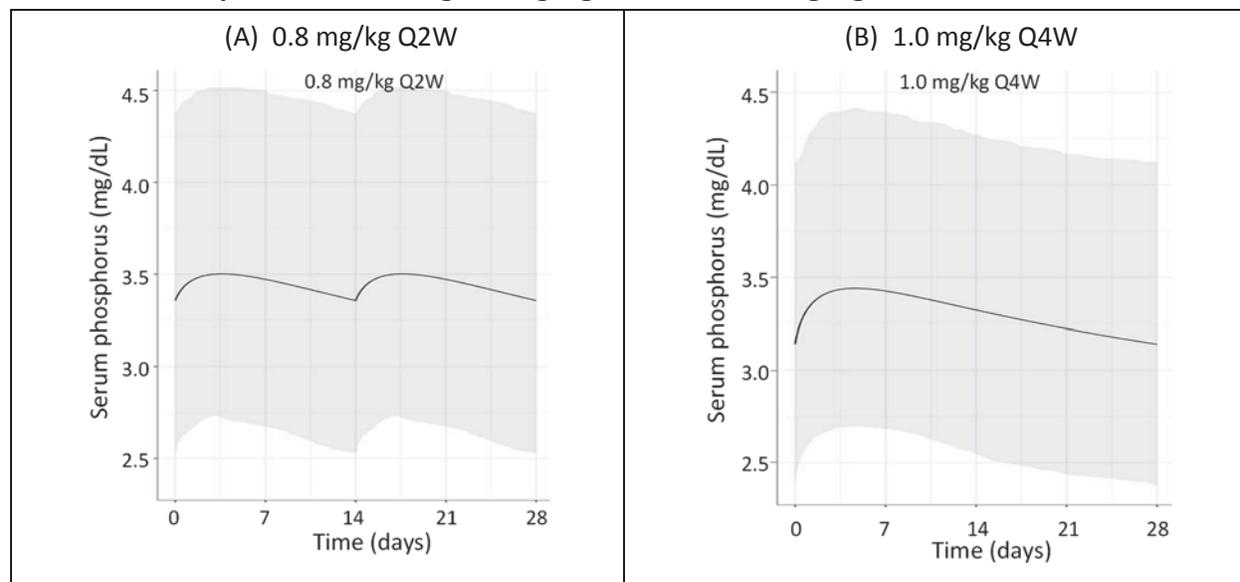
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P10, 10th percentile; P50, 50th percentile; P90, 90th percentile; LOESS, locally weighted scatter plot smoothing.
(Source of data: (A) and (B), applicant's response to IR on November 10, 2017; (C), Reviewer's independent analysis)

Serum phosphorus concentrations in adolescent XLH patients were simulated using the population PK/PD model developed with data from pediatric XLH patients 1 to 12 years of age and the predicted burosumab concentrations simulated using the population PK model in adolescent subjects. **Figure 20** shows the simulated steady-state serum phosphorus concentration-time profiles in the first 4 weeks following burosumab treatment in adolescent XLH patients receiving 0.8 mg/kg Q2W and 1.0 mg/kg Q4W dose regimens, respectively. The simulated serum phosphorus levels overall indicate that both 0.8 mg/kg Q2W and 1.0 mg/kg Q4W regimens could reasonably achieve normal serum phosphorus levels in adolescent XLH patients with appropriate dose titration. We recommend the 0.8 mg/kg Q2W dosing regimen in adolescent XLH patients for the following considerations:

- Approximately 58% and 42% of the simulated minimum of serum phosphorus levels were higher than the lower bound of normal serum phosphate range of 3.2 mg/dL for the 0.8 mg/kg Q2W and 1.0 mg/kg Q4W dosing regimens, respectively. This suggests a favorable therapeutic effect in achieving normal serum phosphorus level for the 0.8 mg/kg Q2W dosing regimen in comparison to the 1.0 mg/kg Q4W dosing regimen.
- Approximately 1.6% and 1.0% of the simulated maximum of serum phosphorus levels were higher than 5.0 mg/dL for the 0.8 mg/kg Q2W and 1.0 mg/kg Q4W dosing regimens, respectively. This suggests that the 0.8 mg/kg Q2W would not significantly increase the risk of treatment-induced hyperphosphatemia in comparison to the 1.0 mg/kg Q4W dosing regimen.
- The efficacy and safety of the 0.8 mg/kg Q2W dosing regimen have been demonstrated in pediatric XLH patients 1 to 12 years of age.

Figure 20. Simulated steady-state concentration-time profiles of serum phosphorus in adolescent XLH patients receiving 0.8 mg/kg Q2W and 1.0 mg/kg Q4W burosumab



Dose levels were rounded to the nearest 10 mg with maximum of 90 mg. Black lines represent the mean values and the gray shaded area represent 90% CI interval. (Source of data: Figure 4, applicant's response to IR on November 10, 2017)

Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No, there is no need for an alternative dosing regimen for subpopulations based on intrinsic factors.

Population PK analysis identified body weight as a significant covariate on burosumab PK. However, because dosing of burosumab is based on body weight and individually titrated to achieve normal serum phosphorus levels, we do not recommend further dose individualization based on body weight. Body weight did not show an impact on efficacy in burosumab XLH clinical trials and therefore no additional regimen or management strategy is necessary.

Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

As this is a monoclonal antibody, drug interaction studies have not been conducted with burosumab. Burosumab is a human monoclonal antibody that is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Therefore, direct drug interactions between burosumab and small molecule drugs that are metabolized by cytochrome P450 (CYP) enzymes are unlikely. In response to Agency's information request, a literature search by the applicant did not identify mechanistic basis for

pharmacodynamic- or disease-drug-drug interactions for burosumab in adult or pediatric subjects with XLH. Based on this information, no clinically relevant drug-drug interactions were identified that require further assessment.

6.4. Clinical Pharmacology Appendices

6.4.1. Summary of Bioanalytical Method Validation and Performance

PK assays: bioanalytical methods for determination of burosumab concentrations in human serum

The applicant used two assays for measurement of serum burosumab concentrations: an enzyme-linked immunosorbent assay (ELISA) and an electrochemiluminescent (ECL)-based bridging immunoassay. Both the ELISA the ECL assays used an identical pair of specific monoclonal antibodies to burosumab as capture and detection agents. The ECL assay was validated and used in two separate laboratory locations. The laboratory locations and associated clinical studies for the two PK assays are summarized in **Table 19**. The assay validation parameters and performance characteristics are summarized in **Table 20**.

Table 19. PK Assays Used in Burosumab Clinical Studies

Assay	Company	Location	Studies Supported	Assay Coating Reagent	Assay Detection Reagent
ELISA	Kyowa Hakko Kirin California, Inc. (KKC) ²	La Jolla, CA	KRN23-US-02, KRN23-INT-001, KRN23-INT-002	Anti-KRN23 idiotype Ab (599 84-2)	Biotinylated anti-KRN23 antibody (132-5* Biotin)
ECL Assay	(b) (4)	(b) (4)	UX023-CL201	Anti-KRN23 idiotype Ab (599 84-2)	Ruthenylated anti-KRN23 Ab (KM4463)
ECL Assay			UX023-CL303, UX023-CL304, UX023-CL205, UX023-CL301, UX023-T-CL201	Anti-KRN23 idiotype Ab (599 84-2)	Ruthenylated anti-KRN23 Ab (KM4463)

*132-5: Former name of KM4463 ECL.

(Source of data: Table 1 of Response to FDA Information Requested Clinical 9 [SDN 12, 11/13/2017])

Table 20. Summary of Validation Results for the Burosumab PK assays

Validation Parameter	Summary of Validation Results		
	ELISA at KKC	ECL* Assay at (b) (4)	ECL* Assay at (b) (4)
Quality Control Sample Levels (ng/mL) used in validation	3000, 600, 50	10000, 7500, 1000, 100, 50	9500, 7500, 4000, 600, 100, 50, 36
Quantitative Range (ng/mL)	50 – 3000	50 – 10,000	36 – 9,500
Minimum Required Dilution (MRD)	1:101	1:200	1:200
Inter-assay accuracy and precision range for all QCs tested in validation	A: 97.2% - 104.7% Overall precision: ≤ 11.6%	A: 100.1% - 106.5% Overall precision: ≤ 8.2%	A: 98.5% - 119.7% Overall precision: ≤ 10%
Intra-assay accuracy and precision ranges for all QCs tested in validation	A: 97.7% - 104.7% Overall precision: ≤ 7.7%	A: 96.3% - 108.3% for all validated QCs Overall precision: ≤ 3.4%	A: 92.8% - 122.4% for QCs at 36, 50, 100, 600, 4000 ng/mL; for 7500 ng/mL, accuracy ranged from 103.5% - 128.9%; for 9500 ng/mL, accuracy ranged from 108.1% to 138.4% Overall precision: ≤ 8.5%
Selectivity	0 and 50 ng/mL KRN23 spiked into 10 individual serum samples; accuracy 88.6% - 107.2%	50 ng/mL KRN23 spiked into 10 individual serum samples; accuracy 87.8% - 104.5%	36 ng/mL and 4000 ng/mL KRN23 spiked into 10 individual serum samples; accuracy 67.6% - 99.2% for 36 ng/mL (80% passed); 82.2 – 95.3% for 4000 ng/mL
Dilutional Linearity	600 µg/mL diluted to 30 µg/mL, 2400 ng/mL, 1200 ng/mL, 600 ng/mL, 300 ng/mL; A: 112.7% -- 120.4%; P: 5.9% - 9.0%	100 µg/mL Dilution factors of 20, 100, 500; A: 90.2% - 94.3%; P: 1.8% - 2.5%	Dilution factors of 2, 5, 10, 25, 50; A: 84.7% - 113.9%; P: ≤ 5.4%
Hook Effect	Not observed at 600 µg/mL and 30 µg/mL	Not observed at 100 µg/mL	Not observed at 950 µg/mL
Stability: Short-term	Up to 24 hours at room temperature (RT) acceptable	Up to 24 hours at RT acceptable	Up to 24 hours at RT acceptable

Validation Parameter	Summary of Validation Results		
	ELISA at KKC	ECL * Assay at (b) (4)	ECL * Assay at (b) (4)
Stability: Freeze/thaw (F/T) cycles	Up to 5 F/T cycles acceptable	Not Done	Up to 3 F/T cycles acceptable
Stability: Long-term	63 days at -20°C; 186 days at -80°C	Not Done	18 months at -80 °C
Hemolysis	Not Done	No effect for 1% hemolysis for 100 ng/mL and 7500 ng/mL KRN23	Not Done
Validation Report Number	23-PK08-006, PK0802 (Long-term stability)	P13-33301	(b) (4)-14-139-008-REP

*Same methodology employed for electrochemiluminescent (ECL) assays validated at designated location
 A: Accuracy (Observed Mean/Nominal Concentration*100); P: Precision [% Coefficient of Variation = (Standard Deviation/Observed Mean) *100].
 (Source of data: Table 2 of Response to FDA Information Requested Clinical 9 [SDN 12, 11/13/2017])

PD assay: bioanalytical methods for determination of serum phosphorous concentrations

The applicant used certified central labs for measurement of serum phosphorus levels in pediatric and adult studies UX023-CL201, UX023-CL205, KRN23-INT-001/KRN23-INT-002, UX023-CL203, UX023-CL303, and UX023-CL304 (**Table 21**).

In these clinical studies, serum phosphorus was analyzed as part of a standard clinical serum chemistry test panel using established CLIA/CAP accredited assays. More specifically, the assay method for inorganic phosphate in serum involves the formation of phosphomolybdate. Phosphomolybdate is measured at 340 nm and is directly proportional to the amount of inorganic phosphate present.

Table 21. Validation Parameters, Reference Values, and Associated Clinical Studies for the Bioanalytical Methods for Measurement of Serum Phosphorus

(b) (4)						
Method	Phosphomolybdate Colorimetric		Phosphomolybdate Colorimetric		Phosphomolybdate Colorimetric	
Validation parameters	Linearity, Precision, Sensitivity, Accuracy/Recovery, Specificity and Stability		Linearity, Precision, Accuracy		Linearity, Precision, Sensitivity, Accuracy, and Stability	
Proficiency testing	Results within acceptable range		Results within acceptable range		Results within acceptable range	
Instruments	Roche Modular, Cobas 8000 analyzers		Olympus AU5400		Siemens ADVIA 1800	
Reference values	Age	(mg/dL)	Age	(mg/dL)	Age	(mg/dL)
	0-1 year	4.2-8.1	13-64 years	2.5-4.5	<1 week	4.0-9.0
	1-5 years	3.2-6.1	65+ years	2.1-4.3	1 week – 2 years	4.0-8.0
	5-10 years	3.2-6.1			3-12 years	3.0-6.0
	10-15 years	3.1-6.0			13-64 years	2.5-4.5
	>15 years	2.2-5.1			>64 years	2.1-4.3
Studies Supported	UX023-CL201, UX023-CL205		KRN23-INT-001/KRN23-INT-002		UX023-CL203, UX023-CL303, UX023-CL304	

(Source of data: Table 2 of Response to FDA Information Requested Clinical 7 Questions 1-4 [SDN 11, 11/03/2017])

Additionally, determination of serum phosphorus concentrations for Study KRN23-US-02 were conducted at local laboratories. Serum phosphorus analyses for study KRN23-001 were conducted as part of the serum chemistry panel at local clinical site laboratories in Japan.

PD assay: Screening FGF23 Assays

The FGF23 assay used to screen subjects as one of the entry criteria into the studies was a commercially available ELISA kit manufactured by Kainos Laboratories Inc. The assay detects and quantitates the full-length (intact) FGF23 molecule. The Kainos ELISA kit can only be used to

test samples when there is no burosumab present, because the coating reagent in the kit and burosumab are specific for a common epitope on the N-terminus of the FGF23 molecule. The Kainos assay is a commercial kit that has been previously been validated by the manufacturer and a partial validation was performed. A summary of the assay validation results for this ELISA is shown in **Table 22**.

Table 22. Summary of Validation Results for the Kainos ELISA Kit for FGF23

Validation Parameter	ELISA Kit at KKC	ELISA Kit at (b) (4)	
Calibration curve standard points (pg/mL)	10, 50, 100, 250, 500 and 800	10, 20, 50, 100, 250, 500 and 800	
%CV of calibrators	0.2 to 32.8%	0.6 to 11.7%	
Intra-assay Precision	1.8 to 27.1% CV	1.0 to 14.3% CV	
Intra-assay Accuracy	-13.7 to -0.9% relative error	81.3 to 118.9% recovery	
Assay range	10 to 800 pg/mL	20 to 600 pg/mL	
Stability		Endogenous FGF23 (~80 pg/ml)	Recombinant FGF23 (~300 pg/ml) spiked
<u>Short term:</u> RT for 4 hrs 4°C for 4 hrs 4°C overnight	Not done	Stable to all storage conditions	Only stable at 4°C for 4 hrs
<u>Freeze and thaw:</u> Samples were frozen at -80 ± 15°C for a minimum of 12 hours and thawed at RT for >= 1 hour before being subjected to a new cycle.	Not done	Stable to 3 F/T cycles	Stable to 1 F/T cycle.
<u>Long term:</u> -80 °C for 1 month	Not done	Stable	Stable
Validation Report	23-A08-004	(b) (4) -14-13-006.01-REP	

(Source of data: Table 2.7.1.1.2.13.1 of Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods of the original BLA)

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PD Assay: Total FGF23 Assays

Following dosing with burosumab, a different assay is used to measure FGF23 in subject serum samples using antibodies which are specific for different epitopes on the FGF23 molecule and do not compete with burosumab. An electrochemiluminescent (ECL) assay based on Meso-Scale Discovery (MSD) methodology was developed and validated for measurement of total FGF23 in human serum. The assay used anti-FGF23 antibody 2C5L as coating reagent and Ruthenium labeled anti- FGF23 Ab (Ru-3C1E) as detection reagent.

A summary of the assay validation results for the ECL assay performed at KKC, (b) (4) is shown in **Table 23**.

Table 23. Summary of Validation Results for the Total FGF23 Assays

Validation Parameter	ECL at KKC	ECL at (b) (4)	ECL at (b) (4)
Studies supported	KRN23-INT-001, KRN23-INT-002	KRN23-001 UX023-CL201	UX023-CL203 UX023-CL205 UX023-CL303 UX023-CL304 UX023-CL301 UX023T-CL201
Calibration curve standard points (pg/mL)	30-12,000	30-12,000	30-12,000
Accuracy and precision	9.7 to 14.2%	100.2-104.3% recovery And 3.9-14.3% CV	100.5 -105.0% recovery And 5.4-26.3% CV
Dilutional linearity up to 125 fold dilution	5% CV	7.5% CV	0.2-15.6% CV
Hook effect	No hook effect	No hook effect	No hook effect
Stability	Stable in assay intermediate matrix for up to 4 hours at RT and 37°C for 2 hours, F/T stability and long-term stability were not done	Stable in the sample diluent buffer for up to 4 hours at RT, F/T stability and long-term stability was not done	Stable at RT for 4.25 hrs, 4°C for 23 hrs, stable to 6 F/T cycles, long term stability (-80 °C for 6 month) was conducted but data was not available when the BLA was submitted.
Validation Report	23-A09-016	P13-33601	(b) (4) -14-139-004-REP

(Source of data: Table 2.7.1.1.2.14.1, Table 2.7.1.1.2.15.1 of Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods of the original BLA)

Immunogenicity assays

This section provides a summary of the drug tolerance levels of immunogenicity assays used for detection of anti-drug antibodies (ADA) in serum samples from burosumab XHL clinical trials that are relevant to clinical pharmacology assessment.

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Except for that immunogenicity samples from study KRN23-US-02 were measured by an ELISA assay, in all other XLH clinical studies antibodies to burosumab were detected using a bridging electrochemiluminescent (ECL) assay. The ECL assay used streptavidin-coated plates and ADA was bridged between biotinylated-burosumab and ruthenylated-burosumab. The immunogenicity assessment strategy involves a three-tiered approach: screening assay, specificity confirmation assay, and titer and neutralizing antibody assays. All serum samples collected for ADA analysis were tested in the screening assay. Samples that tested positive in the screening assay were analyzed in the confirmatory format to test for specificity against burosumab. Samples identified as positive in the confirmatory assay were then further characterized in the titer and neutralization (NAb) assays.

Because only ADA positive samples were further tested for neutralizing activity and because no subjects showed treatment-emergent ADA in XLH clinical trials using current assays, the drug tolerance level for the neutralizing antibody assay is not further discussed in the clin pharm review. See Product Quality section of this multi-disciplinary review for additional information regarding the performance and validation of the immunogenicity assays assessed by OBP immunogenicity reviewer.

An overview of the assay sensitivity, drug tolerance level of the ADA assays and associated clinical studies are presented in **Table 24**. Overall, the drug tolerance levels were lower than the steady state drug concentrations observed in XLH clinical studies indicating the limitation of the current immunogenicity assays to detect ADA in the presence of burosumab in serum samples from XLH clinical studies.

Table 24. Overview of Assays Used for Detection of ADA

ADA Assay (Site)	Clinical Studies	Assay Sensitivity	Drug tolerance [Validation report]	Referenced Steady-State PK information
ELISA	KRN-23-US-02	1 mcg/mL	Drug tolerance level was not tested. [23-108-007]	In Study UX023-CL201 (pediatric subjects 5-12 yrs of age), mean \pm SD serum burosumab concentration at Week 64 (trough) was 15.85 \pm 9.39 mcg/mL in the Q2W group and 8.53 \pm 3.97 mcg/mL in the Q4W group.
ECL (KKC)	KRN23-INT-001 KRN23-INT-002	42.8 ng/mL	0.5 mcg/mL burosumab at 500 ng/mL positive control ADA. [23-110-020]	
ECL (b) (4)	KRN23-001 UX023-CL201	19.2 ng/mL	0.25 mcg/mL burosumab at 200 ng/mL positive control ADA. 4 mcg/mL burosumab at 2000 ng/mL positive control ADA. [P13-33401], [P15-33407]	In Study UX023-CL303 (adult subjects), mean \pm SD steady state peak (Week 20) and trough (Week 24) were 10.09 \pm 4.28 mcg/mL and 5.83 \pm 3.43 mcg/ml, respectively.
ECL (b) (4)	UX023-CL303 UX023-CL304 UX023-CL301 UX023-CL205 UX023-CL203 UX023-CL201	20.6 ng/mL	0.47 mcg/mL burosumab at 100 ng/mL positive control ADA 3.75 mcg/ml burosumab at 2000 ng/ml positive control ADA L (b) (4)-14-139-010-REP]	

(Source of data: Table 2.7.1.1.2.5.1 and Table 2.7.1.1.2.9.1, Module 2.7.1, Summary of Biopharmaceutical Studies and Associated Analytical Methods).

6.4.2. Biopharmaceutics

The applicant used three liquid formulations differing in burosumab concentrations or strengths, i.e., 30 mg/mL, 10 mg/mL and 2 mg/mL, in burosumab XLH clinical trials. **Table 25** below summarizes the total number of administrations and percentage of use for each of the formulation strengths in individual studies. The 2 mg/mL formulation was only used in Study KRN23-US-02 in which burosumab was administered via IV or SC injection. In all other clinical studies, burosumab was administered by SC administration using the 10 mg/mL formulation and/or the 30 mg/mL formulation. The 10 mg/mL and 30 mg/mL formulations have the same excipient composition and concentration that have remained the same during the clinical

studies and in the commercial formulations. Refer to the Product Quality review for more details of the formulation composition related analytical data.

Table 25. Percent Use of Product Strength in Individual Burosumab Trials

XLH Subject Population	Study	Number of SC Administration (%) Product Strength		
		2 mg/mL	10 mg/mL	30 mg/mL
Adult	KRN23-US-02	3 (25.0%)	9 (75.0%)	
	KRN23-INT-001		115 (100%)	
	KRN23-INT-002		156 (64.7%)	85 (35.3%)
	UX023-CL203			328 (100%)
	UX023-CL303			836 (100%)
Pediatrics	UX023-CL201		129 (6.1%)	2002 (93.9%)
	UX023-CL205		37 (18.9%)	159 (81.1%)
Overall		3 (0.1%)	446 (11.6%)	3410 (88.4%)

(Source of data: Table 2.7.2.3.4.1 of Module 2.7.2)

PK comparability between 10 mg/ml and 30 mg/ml formulations: Studies KRN23-INT-001/ KRN23-INT -002

In Study KRN23-INT-001, all subjects started burosumab treatment using the 10 mg/ml formulation. During the extension phase of Study KRN23-INT-001 (named KRN23-INT-002), burosumab administration was switched to using the 30 mg/ml formulation. The same burosumab dosing regimen (Q4W) was used during these two studies for each subject.

The FDA reviewer conducted an exploratory PK comparability assessment between the two formulations using the mean dose-adjusted steady-state trough concentrations before and after the formulation switch in Studies KRN23-INT-001/-002. Due to complexity of the study design and the available PK data, a total of 12 subjects were identified to have evaluable PK data from both the 10 mg/ml and 30 mg/ml formulations for PK comparability assessment. The comparative PK data showed that the two formulations had similar PK because the geometric mean ratio of the burosumab concentration was close to the value of 1 (**Table 26**). However, the 90% confidence interval for the point estimate was not within the 80% to 125% boundaries of the bioequivalence criteria which is not unexpected because of the small sample size.

Table 26. PK comparability analysis results between 10 mg/mL and 30 mg/mL formulations (FDA reviewer’s analysis)

Parameters	Geometric Mean (CV%)		Geometric LSMean (SE)		Ratio of LSMean (90% CI)
	Test (10 mg/ml) (n=12)	Reference (30 mg/ml) (n=12)	Test (10 mg/ml) (n=12)	Reference (30 mg/ml) (n=12)	
Dose-Adjusted Steady-State Trough Concentrations	62.1 (65.8%)	58.7 (93.2%)	62.1 (11.79)	58.7 (15.8)	1.057 (66.4%-168.4%)

Bioequivalence testing was conducted using WINNONLIN Phoenix 64 based on individual subject mean Ctrough concentrations for each formulation. Note that due to the unbalanced nature of Ctrough concentrations reported, a majority of subjects had more Ctrough datapoints with 10 mg/ml formulation than 30 mg/ml formulation.

The applicant also conducted PK comparability assessment between the 10 mg/mL and 30 mg/mL formulations based on the total number of PK samples in the same 12 subjects with evaluable PK data. In the applicant’s assessment, the statistical comparison of Ctrough between the two formulations was conducted using the sample size of all evaluable Ctrough concentrations (i.e., 52 samples related to the 10 mg/mL formulation and 35 samples related to the 30 mg/mL formulation). The applicant’s PK analysis showed that the two formulation had similar PK and the 90% confidence intervals for the point estimate was within the 80-125% BE criteria **Table 27**. The applicant’s analysis was verified by FDA reviewer.

Table 27. PK comparability analysis results between 10 mg/mL and 30 mg/mL formulations (The applicant’s analysis)

Parameter	Geometric LSMean (SE)		Geometric Mean (CV%)		Ratio of LSMean (Test/Reference)	90% CI	Intra-Subject CV%
	Test (10 mg/mL)	Reference (30 mg/mL)	Test (10 mg/mL)	Reference (30 mg/mL)			
Dose-Adjusted Trough Concentrations	59.7 (11.2)	57.0 (10.8)	72.2 (62.7)	50.9 (77.6)	104.7	92.9, 118	29.1

(Source of data: Table 2.7.2.3.4.1.1 of Module 2.7.2)

Multi-Disciplinary Review
BLA 761068
(burosumab - twza)

Reviewer Comments:

The biopharmaceutics information and available PK data did not identify any evidence to indicate that the 10 mg/mL and 30 mg/mL formulations may perform differently for subcutaneous administration of burosumab. Examination of the individual PK data showed that the serum burosumab concentrations had remained reasonably stable during switch of two formulations. Furthermore, both the 10 mg/mL and 30 mg/mL formulations have demonstrated clinical efficacy in upregulation serum phosphorus levels across clinical trials, which would support the approval for both formulations. The proposed 20 mg/mL formulation, which was not tested in clinical trials, is also approvable because it has the same excipient composition/concentration as the 10 mg/mL and 30 mg/mL formulations. Nonetheless, because dosing of burosumab is titrated based on the targeted normal serum phosphorus levels, the remaining PK comparability uncertainties (if any) among these formulations would not affect the effective use of the drug product.

6.4.3. Individual Clinical Pharmacology Study Summary

Study KRN23-US-02

Study KRN23-US-02 was a Phase 1, double-blind, randomized, placebo-controlled, single-dose escalation study. The study characterized the PK profile of burosumab following a single IV or SC administration in adult XLH subjects. The 5 dose levels evaluated in the burosumab IV treatment arm were 0.003, 0.01, 0.03, 0.1, and 0.3 mg/kg. The 4 dose levels evaluated in the burosumab SC treatment arm were 0.1, 0.3, 0.6, and 1.0 mg/kg. A total of 29 patients had valid KRN23 serum concentration data and were included in the PK analysis.

PK Results

The mean PK parameters following IV administration of KRN23 are summarized in **Table 28**.

Table 28. Summary of Pharmacokinetic Parameters Following a Single-Dose IV Administration of KRN23

Dose (mg/kg)		t _{max} (hr)	C _{max} (µg/mL)	AUC _{0-t} (µg.hr/mL)	AUC _{0-∞} (µg.hr/mL)	t _{1/2} (hr)	CL _{IV} (mL/hr/kg)	V _{ss} (mL/kg)
0.003	n=3							
	Mean	1.84	0.0693	1.19	-	-	-	-
	SD	0.577	0.00712	0.441	-	-	-	-
	Min	1.17	0.0617	0.686	-	-	-	-
	Median	2.17	0.0705	1.35	-	-	-	-
	Max	2.17	0.0758	1.52	-	-	-	-
	CV%	31	10	37	-	-	-	-
0.01	n=3							
	Mean	1.50	0.256	33.1	52.0	199	0.206	51.7
	SD	0.577	0.016	8.93	15.3	83.9	0.0727	10.1
	Min	1.17	0.240	23.3	34.5	105	0.161	42.7
	Median	1.17	0.255	35.2	59.4	225	0.168	49.8
	Max	2.17	0.272	40.8	62.2	267	0.290	62.6
	CV%	38	6	27	29	42	35	20
0.03	n=3							
	Mean	1.19	1.04	131	156	180	0.196	43.6
	SD	0.970	0.202	18.4	28.7	98.8	0.0326	15.8
	Min	0.230	0.824	118	139	118	0.158	33.3
	Median	1.17	1.09	124	140	129	0.214	35.8
	Max	2.17	1.22	152	189	294	0.216	61.7
	CV%	82	19	14	18	55	17	36
0.1	n=5							
	Mean	1.19	2.95	620	666	296	0.156	56.4
	SD	0.736	0.927	131	144	65.9	0.0362	12.0
	Min	0.170	2.27	460	474	185	0.117	42.5
	Median	1.17	2.82	637	700	307	0.143	64.5
	Max	2.25	4.54	808	854	351	0.211	65.6
	CV%	62	31	21	22	22	23	21
0.3	n=3							
	Mean	1.19	9.20	2050	2170	273	0.140	57.2
	SD	0.0321	1.83	331	312	29.1	0.0212	14.5
	Min	1.17	7.13	1670	1830	241	0.123	46.5
	Median	1.18	9.86	2160	2230	278	0.135	51.5
	Max	1.23	10.6	2300	2450	299	0.164	73.7
	CV%	3	20	16	14	11	15	25

AUC_{0-τ} = area under the serum concentration vs. time curve from 0 to 't' hours; AUC_{0-∞} = AUC from zero to infinity; CL_{IV} = clearance; C_{max} = maximum serum concentration; CV% = coefficient of variance, expressed in percent; Max = maximum; Min = minimum; t_{max} = time to peak plasma concentration; SD = standard deviation; t_{1/2} = half life; V_{ss} = volume of distribution at steady state; "-" Not calculated because t_{1/2} could not be estimated.

(Source of data: Table 11.4.5-1 of the Clinical Study Report)

The mean PK parameters following SC administration of KRN23 are summarized in **Table 29**.

Table 29. Summary of Pharmacokinetic Parameters Following a Single-Dose SC Administration of KRN23 (N=12)

Dose (mg/kg)		t _{max} (hr)	C _{max} (µg/mL)	AUC _{0-t} (µg.hr/mL)	AUC _{0-∞} (µg.hr/mL)	t _{1/2} (hr)
0.1	n=3	n=3	n=3	n=3	n=3	n=3
	Mean	271	0.755	503	599	423
	SD	91.0	0.266	121	157	119
	Min	167	0.453	383	483	294
	Median	311	0.858	501	535	448
	Max	336	0.955	625	777	529
	CV%	34	35	24	26	28
0.3	n=3	n=3	n=3	n=3	n=2	n=2
	Mean	192	3.00	2180	2780	362
	SD	110	1.01	418	-	-
	Min	96.0	1.93	1790	2400	304
	Median	168	3.15	2130	2780	362
	Max	311	3.93	2620	3150	420
	CV%	57	34	19	-	-
0.6	n=3	n=3	n=3	n=3	n=3	n=3
	Mean	216	3.62	2750	3180	322
	SD	42.2	1.94	1450	1680	40.8
	Min	167	1.42	1080	1240	294
	Median	239	4.35	3520	4060	303
	Max	241	5.10	3650	4230	369
	CV%	20	54	53	53	13
1.0	n=3	n=3	n=3	n=3	n=2	n=2
	Mean	272	7.71	5310	6900	448
	SD	124	2.07	556	-	-
	Min	167	6.40	4880	6590	296
	Median	242	6.64	5120	6900	448
	Max	409	10.1	5940	7210	601
	CV%	46	27	10	-	-

AUC_{0-τ} = area under the serum concentration vs. time curve from 0 to 't' hours; AUC_{0-∞} = AUC from zero to infinity; CLIV = clearance; C_{max} = maximum serum concentration; CV% = coefficient of variance, expressed in percent; Max = maximum; Min = minimum; t_{max} = time to peak plasma concentration; SD = standard deviation; t_{1/2} = half life. "- Not calculated for sample size of ≤ 2. This table does not include Patient (b) (6).

(Source of data: Table 11.4.5-2 of the Clinical Study Report)

Following a single SC administration of KRN23, the mean t_{max} values ranged from 8 to 11 days, the mean t_{1/2} ranged from 13 to 19 days, and the mean AUC values appeared to increase in a dose-proportional manner at the tested doses from 0.1 to 1.0 mg/kg.

The absolute bioavailability of KRN23 was estimated to be 90 and 128%, respectively, at 0.1 and 0.3 mg/kg doses based on mean AUC_{0-∞} values. However, the number of subjects was too small to make a definitive determination of bioavailability.

Study KRN23-001

Study KRN23-001 was a Phase 1, open-label, single-dose escalation study that evaluated the PK and PD of burosumab after single-dose SC administration of burosumab at doses of 0.3, 0.6, and 1.0 mg/kg in adult XLH subjects in Japan and Korea.

The PK results are summarized in **Table 30**. After single SC administration of burosumab at doses of 0.3, 0.6, and 1.0 mg/kg, serum burosumab concentrations reached peak concentrations (C_{max}) at approximately 7 days, the mean $t_{1/2}$ were approximately 12 to 14 days, and the AUCs increased in a dose-proportional manner.

Table 30. Summary of Pharmacokinetic Parameters of Burosumab in Study KRN23-001

Cohort	Burosumab Dose (mg/kg)	n	C_{max} (µg/mL)	T_{max} (hr)	AUC_{0-t} (µg·h/mL)	$AUC_{0-∞}$ (µg·h/mL)	$t_{1/2}$ (hr)	CL/F (mL/h/kg)	V_z/F (mL/kg)
1	0.3	6	1.71 (0.51)	166 (46.5-168)	1020 (300)	1180 (370)	289 (121)	0.277 (0.096)	107 (38)
2	0.6	5	2.95 (0.67)	167 (165-334)	1940 (620)	2220 (920)	315 (131)	0.309 (0.123)	122 (8)
3	1.0	7	5.19 (2.12)	166 (93.5-168)	3330 (1320)	3770 (1670)	336 (85)	0.307 (0.116)	143 (49)

PK parameter values are reported as mean (SD), except that T_{max} values are reported as median (range).

(Source of data: Table 14.2-1.4 of the Clinical Study Report)

Studies KRN23-INT-001, KRN23-INT-002, and UX023-CL203 (The Open-label Multiple Ascending Dose Study with its Two Open-label Extension Studies in Adult XLH Patients)

Study KRN23-INT-002 enrolled adult XLH patients who participated Study KRN23-INT-001. Study UX023-CL203 enrolled adult XLH patients who participated Study KRN23-INT-001 or Study KRN23-INT-002, for long-term follow up, and is still ongoing. The defined serum phosphorus target range in these three studies was 2.5-3.5 mg/dL and the upper limit of normal for age is 4.5 mg/dL.

Study KRN23-INT-001 was a Phase 1/2, open-label, dose-escalation study of KRN23 in adult subjects with XLH. After screening, all eligible subjects were treated with up to 4 doses (1 dose every 28 days, SC administration) of KRN23 using stepwise dose-escalation from 0.05 mg/kg → 0.1 mg/kg → 0.3 mg/kg → 0.6 mg/kg. Intra-subject dose-escalation was based on serum phosphorus levels guided by a dose-escalation algorithm and other safety observations (i.e., adverse event [AE] monitoring, safety laboratory parameters, immunogenicity, and physical examination findings).

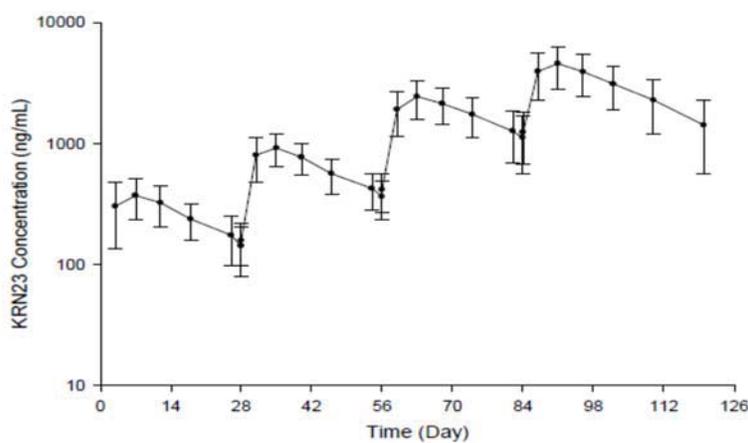
Subjects who satisfactorily completed study KRN23-INT-001 were eligible to enter the open-label extension phase (also called Study KRN23-INT-002). In this study, each subject received repeat-doses of KRN23 (up to 12 doses) administered SC once every 28 days. The initial KRN23 dose in this extension study was the same KRN23 dose that the subject received on Day 84 in Study KRN23-INT-001, unless the subject's serum phosphorus level was out of the prespecified range for certain time points. For the subsequent doses, dose could be titrated up or down primarily based on serum phosphorus levels. The allowed dosing steps were 0.05, 0.1, 0.3, 0.6 or 1.0 mg/kg.

Study UX023-CL203 enrolled adults with XLH who previously participated in study KRN23-INT-001 or KRN23-INT-002 to collect additional information on the safety, immunogenicity, and pharmacodynamic (PD) response with long-term administration of KRN23 in this patient population. After all Screening and Baseline assessments were completed, subjects received starting doses of KRN23 (0.3, 0.6, or 1.0 mg/kg every 4 weeks) that matched their last dose in study KRN23-INT-001 or KRN23-INT-002 and were based on subjects' body weight at Day 0. KRN23 injections were administered every 4 weeks and body weight was reassessed periodically for dose adjustments as needed. Dose could be titrated up or down primarily based on serum phosphorus levels. The allowed dosing steps were 0.3, 0.6 or 1.0 mg/kg.

Results from Study KRN23-INT-001

The mean serum concentrations of KRN23 in Study KRN23-INT-001 are displayed in **Figure 21**. A summary of PK parameters for KRN23 from Study KRN23-INT-001 are provided in **Table 31** and **Table 32**.

Figure 21. Mean (\pm SD) KRN23 Concentration Over Time (During the 4 Dosing Intervals) in Study KRN23-INT-001



(Source of data: Figure 11.4-9 of the Clinical Study Report)

Table 31. PK summary of Intra-Dose-Escalation (Starting Dose 0.05 mg/kg SC) of KRN23 Every 28-days to Adult Subjects with XLH in Study KRN23-INT-001

Dosing Interval	Statistic	$t_{\max,n}$ (day)	$C_{\max,n}$ (ng/mL)	$C_{\min,n}$ (ng/mL)	AUC_n (ng·day/mL)
1	N	27	27	27	27
	Mean (SD)	8.50 (2.90)	386 (145)	147 (53.4)	7260 (2630)
	Min, Max	2.98, 14.9	193, 688	60.7, 253	2980, 13200
	Median	7.94	374	139	6560
	CV%	34	38	36	36
2	N	27	27	27	27
	Mean (SD)	7.04 (1.71)	947 (307)	364 (130)	17900 (5310)
	Min, Max	3.95, 11.9	356, 1710	119, 662	6500, 28600
	Median	6.96	870	373	16900
	CV%	24	32	36	30
3	N	27	27	27	27
	Mean (SD)	7.45 (3.83)	2490 (843)	1080 (587)	50900 (18000)
	Min, Max	1.96, 19.9	421, 3950	104, 2560	9500, 98000
	Median	6.95	2540	1080	48300
	CV%	51	34	54	35
4	N	26	26	26	26
	Mean (SD)	7.00 (3.22)	4750 (1800)	1470 (827)	109000 (40600)
	Min, Max	2.87, 15.0	1030, 8110	166, 2890	23800, 178000
	Median	6.89	5030	1310	103000
	CV%	46	38	56	37

AUC_n = area under the serum concentration-time curve in n-th dosing interval; $C_{\max,n}$ = maximum serum concentration during the dosing interval; $C_{\min,n}$ = predosed observed serum concentration at the end of n-th dosing interval; CV% = coefficient of variation, percent; Max = maximum; Min = minimum; SD = standard deviation; $t_{\max,n}$ = time of maximum observed serum concentration during n-th dosing interval; XLH = X-linked hypophosphatemia.

(Source of data: Table 11.4.1-5 of the Clinical Study Report)

Table 32. PK summary of Intra-Dose-Escalation (Starting Dose 0.05 mg/kg SC) of KRN23 Every 28-days to Adult Subjects with XLH in Study KRN23-INT-001(Data from all 4 Dosing Intervals)

Statistic	AUC _{last} (µg·hr/mL) ^a	AUC _{inf} (µg·hr/mL) ^b	t _{1/2} (day)	CL/F (mL/hr/kg) ^c	V _Z /F (mL/kg) ^d	t _{last} (day)
N	27	27	27	27	27	27
Mean	4340	5240	16.4	0.186	98.3	122
SD	1320	1880	5.83	0.0780	34.6	2.79
Min	1340	1570	5.58	0.0835	51.2	116
Median	4520	5170	15.8	0.161	86.1	122
Max	6450	8990	29.5	0.472	212	125
CV%	30	36	35	42	35	2

AUC_{last} = area under the serum concentration-time curve from time 0 to the time of last measurable concentration over all the dosing interval (Day120 or early withdrawal) determined using the linear trapezoidal rule; AUC_{inf} = area under the serum concentration-time curve from 0 to infinity over all the dosing interval determined using the linear trapezoidal rule; t_{1/2} = terminal elimination half-life after 4th dosing; CL/F = apparent serum clearance; t_{1/2} = terminal elimination half-life after fourth dosing interval; V_Z/F = apparent volume of distribution; t_{last} = the time of last measurable concentration over all the dosing interval.

a: AUC_{inf} was calculated as $AUC_{last} + C_{last}/\lambda_{zn}$ where C_{last} is the last measurable concentration over all the dosing interval and λ_{zn} is the rate constant associated with elimination phase.

b: t_{1/2} was calculated as $\ln 2/\lambda_{zn}$.

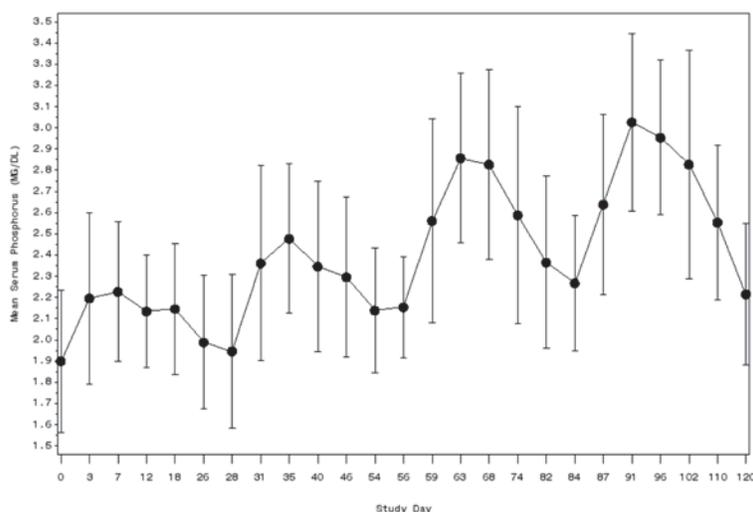
c: CL/F was calculated as Total Dose over 120 days of treatment/AUC_{inf}.

d: V_Z/F was calculated as CL/F and t_{1/2}.

(Source of data: Table 11.4.1-6.of the Clinical Study Report)

Mean serum phosphorus levels in Study KRN23-INT-001 are displayed in **Figure 22**.

Figure 22. Mean (± SD) Serum Phosphorus Values by Study Day in KRN23-INT-001



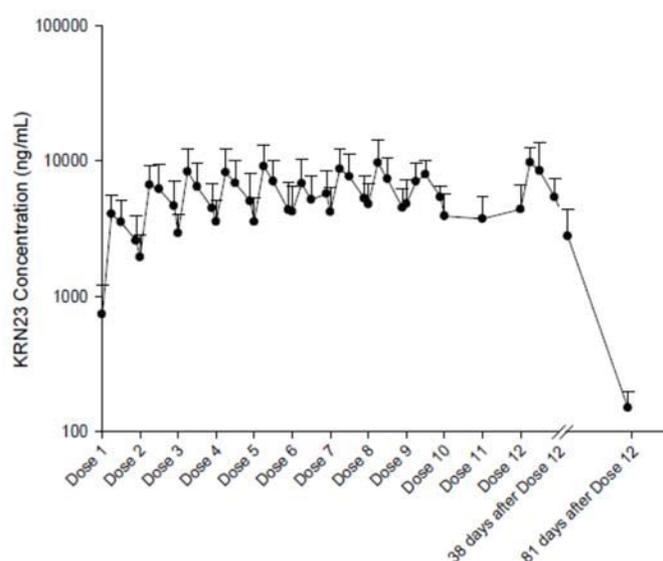
(Source of data: Figure 11.4-1 of the Clinical Study Report)

Results from Study KRN23-INT-002

The starting KRN23 dose ranged from 0.3 to 1.0 mg/kg during Dosing Interval 1 with a mean \pm SD of 0.54 ± 0.20 mg/kg. During Dosing Intervals 2 and 3, the mean \pm SD doses increased to 0.77 ± 0.27 and 0.73 ± 0.28 mg/kg, respectively. The mean KRN23 doses in Dosing Intervals 4 to 12 were stable and ranged from 0.81 to 0.88 mg/kg. Doses for individual subjects were stable from Dosing Intervals 4 to 12 and $\geq 85\%$ of subjects received KRN23 dose of 0.6 or 1.0 mg/kg (Table 12.1-1 of the Clinical Study Report).

The mean serum concentrations of KRN23 are illustrated in **Figure 23**.

Figure 23. Mean (+SD) Serum Concentrations for KRN23 Following Repeat (12 Dosing Intervals) Subcutaneous Administrations of KRN23 Every 28-days to Adult Subjects with XLH (N=22) in Study KRN23-INT-002



(Source of data: Figure 11.4-7 of the Clinical Study Report)

Prior to dosing in both studies (KRN23-INT-001 and KRN23-INT-002), all subjects had serum phosphorus levels ≤ 2.5 mg/dL. During each 28-day dosing interval in KRN23-INT-002, maximum serum phosphorus levels were achieved on Day 7 or 14 for subjects treated with KRN23 (Table 11.4.1-1 of the Clinical Study Report). On Day 7 or 14 after the first KRN23 treatment (Dosing Interval 1), the serum phosphorus levels of a large majority of subjects (17 to 18 subjects, 77.3% to 81.8%) had increased from ≤ 2.5 mg/dL into the target range of > 2.5 to ≤ 3.5 mg/dL. Peak Day 7 or 14 serum phosphorus levels remained in the target range of > 2.5 to ≤ 3.5 mg/dL for 44.4% to 81.8% of the 22 KRN23-treated subjects for all 12 dosing intervals (Table 11.4.1-1). The percentage of subjects with serum phosphorus levels within the target range was generally similar on Days 7 and 14 for most dosing intervals throughout the study period. Peak serum phosphorus levels on Day 7 or 14 were increased into the > 3.5 to ≤ 4.5 mg/dL range in 1

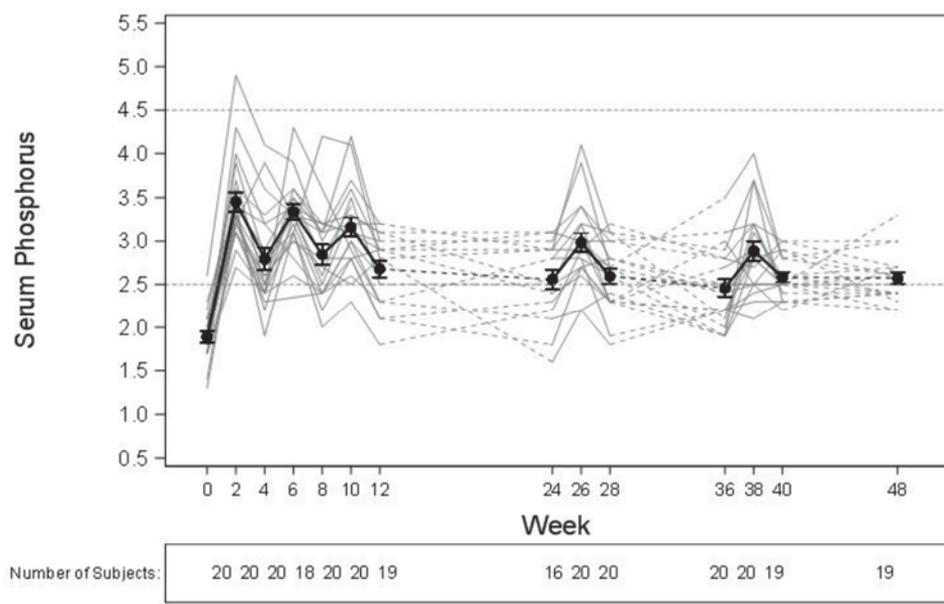
to 3 KRN23-treated subjects (4.5% to 16.7%) throughout the study; no serum phosphorus level > 4.5 mg/dL was reported for any subject at anytime point.

Results from Study UX023-CL203

Mean (SD) serum concentrations of KRN23 at Week 48 were 4771 (2348) ng/mL (range: 1616 to > 9500 ng/mL [upper limit of quantitation]) (Table 14.99.3.7.1, Listing 16.99.2.5.1 of the Clinical Study Report).

Mean serum phosphorus at Baseline was 1.89 mg/dL (range, 1.3–2.6 mg/dL) and serum phosphorus increased after the first dose of KRN23. All 20 (100%) subjects had at least one serum phosphorus level in the normal range during KRN23 dosing, as shown in **Figure 24**.

Figure 24. Individual and Mean (\pm SE) Serum Phosphorus Levels (mg/dl)



SE = standard error.

Note: n = 16 at Week 24 because the laboratory cancelled four samples due to insufficient centrifugation

Note: 1.0 mg/dL = 0.323 mmol/L

(Source of data: Figure 10.1.1.1 of the Clinical Study Report)

Study UX023-CL303 (The Placebo-controlled Phase 3 Study in Adult XLH Patients)

Study UX023-CL303 is an ongoing, randomized, double-blind, placebo-controlled, multicenter, Phase 3 study of KRN23 in adults with XLH. The primary efficacy endpoint for this study was the proportion of subjects achieving mean serum phosphorus concentrations above the lower limit of normal (LLN; 2.5 mg/dL) at the midpoint of the dose interval, as averaged across dose cycles between baseline and Week 24.

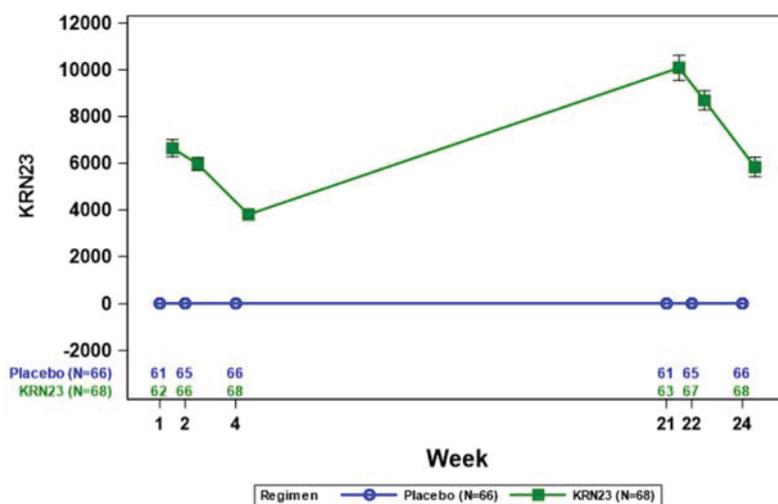
Subjects began treatment with an SC injection of 1.0 mg/kg KRN23, rounded to the nearest 10 mg, administered Q4W, up to a maximum dose of 90 mg. The dose remained fixed for the duration of the study, but can be adjusted in the event of high serum phosphorus (>5.0 mg/dl, or two consecutive levels >4.5 mg/dl), or body weight change >20% from the baseline.

In both treatment and placebo groups, the observed median weight-based dose of blinded study drug was 1.0 mg/kg (mean: 0.99 mg/kg; range: 0.6–1.1) at the Baseline Visit and remained 1.0 mg/kg (mean: 0.97-0.98 mg/kg; range: 0.3–1.1) at all post-baseline visits through the 24 week double-blind period. At Week 24, when all subjects began receiving open-label KRN23, the median weight-based dose of KRN23 was 1.0 mg/kg in both treatment groups; through the data cutoff, the median dose was 1.0 or 0.9 mg/kg in both groups.

Serum KRN23 concentrations (PK)

Samples for analysis of KRN23 serum concentrations were obtained throughout the study at time points representing approximate peak (Weeks 1, 2, 21, and 22) and trough (Weeks 4 and 24) exposure levels. Mean serum KRN23 concentrations in the KRN23 group increased with multiple Q4W dosing. Mean \pm SD values of maximum and minimum serum concentrations of KRN23 in the first dose cycle (Weeks 0-4) were 6644 \pm 2911.7 ng/mL (at Week 1) and 3804 \pm 1621.6 ng/mL (at Week 4), respectively. In the last dose cycle (Weeks 20-24), the respective concentrations were 10085 \pm 4275.6 ng/mL (at Week 21) and 5832 \pm 3434.1 ng/mL (at Week 24). The concentration-time profile of KRN23 during the 24-week treatment period of the study is presented in **Figure 25**.

Figure 25. Mean (\pm SE) Serum KRN23 Concentration (ng/ml) over time (Study UX023-CL303 24 week analysis)

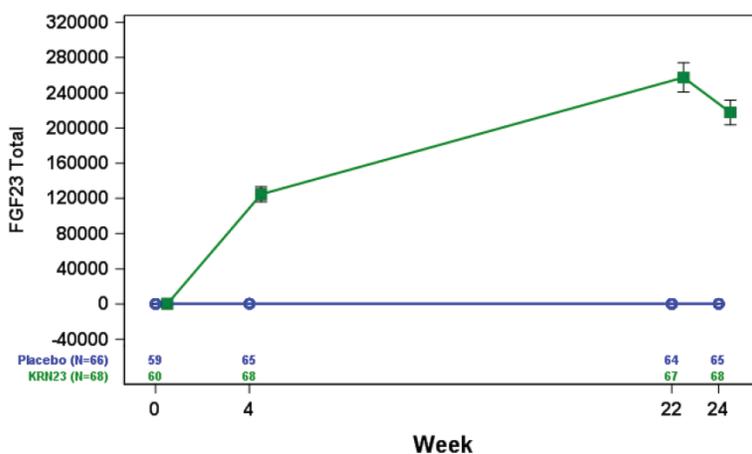


(Source: Figure 11.1 of the Clinical Study Report)

Serum FGF23 Concentrations

Elevations in serum total FGF23 were observed after initiation of KRN23 treatment as shown in **Figure 26**. Mean \pm SE serum total FGF23 increased from 158.69 \pm 40.971 pg/mL in the KRN23 group and 154.08 \pm 37.879 pg/mL in the placebo group at baseline to 217,641.79 \pm 14,021.35 pg/mL in the KRN23 group and 279.19 \pm 76.03) pg/mL in the placebo group at Week 24.

Figure 26. FGF23 Levels (pg/ml) (Mean \pm SE) (Safety Analysis Set)



(Source: Figure 12.7.2.3.1 of the Clinical Study Report)

Study UX023-CL201 (Pediatric Patients 5-12 Years of Age)

Study UX023-CL201 is a randomized, multicenter, open-label, dose finding study of KRN23 in subjects 5 to 12 years of age with XLH. As the first pediatric study of KRN23, the starting doses were low and two dosing frequencies (Q2W and Q4W) were studied. Patients were assigned to one of six dose cohorts, with starting doses of 0.1, 0.2, 0.3 mg/kg Q2W or 0.2, 0.4 or 0.6 mg/kg Q4W. Within each dosing frequency group, the enrollment was staggered.

For both the Q2W and Q4W groups, the target for serum phosphorus was set at 3.5 - 5.0 mg/dL. The defined serum phosphorus normal range for age is 3.2-6.1 mg/dL. The dose was adjusted every 4 weeks based on 2-week post-dose fasting serum phosphorus levels. Dose adjustments were conservative initially (0.1 mg/kg Q2W or 0.2 mg/kg Q4W) and increased to (0.3 mg/kg Q2W and 0.4 mg/kg Q4W) based on Week 16 PD data. The maximum allowed dose was 2.0 mg/kg for both the Q2W and Q4W regimens with a maximum dose of 90 mg. Dose reductions were allowed for serum phosphorus above target range. Rounding of calculated doses to the nearest 10 mg was implemented in protocol 5.

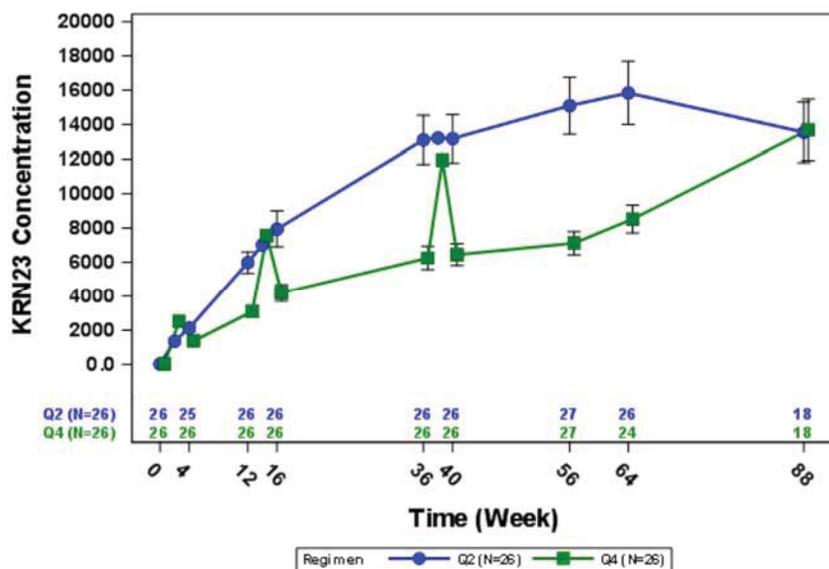
Overall, for subjects received burosumab Q2W, the mean burosumab dose increased from 0.24 mg/kg at Baseline (range: 0.1 to 0.3 mg/kg), to 0.73 mg/kg at Week 16 (range: 0.3 to 1.5 mg/kg), to 0.84 mg/kg at Week 30 (range: 0.4 to 1.8 mg/kg), to 0.90 mg/kg at Week 32 (range:

0.4 to 2.0 mg/kg), to 0.98 mg/kg at Week 40 (range: 0.4 to 2.0 mg/kg), to 1.05 mg/kg at Week 66 (range: 0.4 to 2.0 mg/kg). Starting from Week 68, the mean KRN23 dose per administration had a slight decrease and plateaued at approximately 0.90 mg/kg through Week 88. Between Week 68 and Week 88, the highest dose administered was 1.8 mg/kg. Through Week 62, mean burosumab doses at each study visit were greater in the Q4W group as compared with the Q2W group because of the less frequent dosing schedule. At Week 64 (beginning of the Treatment Extension Period), subjects in the Q4W group switched to Q2W dosing.

Serum KRN23 concentrations (PK)

Pre-dose PK samples were collected for measurement of trough serum KRN23 concentrations. Additional PK samples were collected at Weeks 2, 14, and 38. Mean KRN23 serum trough concentrations increased over time in both dose groups. In general, the Q2W dosing regimen were associated with high serum KRN23 concentrations compared to the Q4W dosing regimen. For example, the Mean \pm SD serum KRN23 concentrations at Week 64 were 15,847 \pm 9385ng/mL in the Q2W dose group and 8526 \pm 3969 ng/mL in the Q4W dose group. Note that at Week 88, the mean serum KRN23 concentrations were similar in the two dose regimen groups because subjects in the Q4W group switched to Q2W dosing at Week 64 (**Figure 27**).

Figure 27. Mean (\pm SE) Serum Concentrations of KRN23 (ng/ml) by Regimen (Safety Analysis Set, N = 52)



Q2 = every 2 weeks; Q4 = monthly

Note: At the beginning of the Treatment Extension Period (Week 64), all subjects received KRN23 Q2W.

Note: Data points are pre-dose concentrations except at Weeks 2, 14, and 38 for the Q4 group which are at the middle of the dosing intervals.

(Source: Figure 10.1.1 of the Clinical Study Report)

Serum FGF23 concentrations

Overall (n =52), mean \pm SD serum total FGF23 concentrations at Baseline were 0.157 \pm 0.094 ng/mL (range: 0.033 to 0.445 ng/mL). Mean \pm SD total FGF23 concentrations were increased to 175 \pm 119 ng/mL at Week 8, 253 \pm 152 ng/mL at Week 16, 429 \pm 209 ng/mL at Week 38, and 470 \pm 253 ng/mL at Week 64. Mean total FGF23 concentrations were greater in the Q2W group (n=26) than in the Q4W group (n=26).

Study UX023-CL205 (Pediatric Patients 1-4 Years of Age)

Study UX023-CL205 is an ongoing randomized, multicenter, open-label study of KRN23 in pediatric subjects (1 to 4 years of age) with XLH. All subjects received KRN23 at a starting dose of 0.8 mg/kg Q2W. The dose may be increased to 1.2 mg/kg at any time if serum phosphorus increases by < 0.5 mg/dL from baseline, and two consecutive measures are below LLN (unless a dose was missed). Dosing was held if serum phosphorus increased above ULN for age. The defined serum phosphorus normal range for age is 3.2 to 6.1 mg/dL.

All subjects received 0.8 mg/kg through Week 20. At Week 22, two subjects had dose adjustments to 1.2 mg/kg based on the protocol-specified dose adjustment criteria that continued through the data cutoff.

Serum KRN23 concentrations (PK)

PK samples for serum concentrations of KRN23 were obtained at Week 1, and pre-dose at Weeks 4 and 12. Serum KRN23 concentrations increased from Week 1 to Week 12. The mean \pm SD serum KRN23 concentrations at Week 1 and Week 12 were 5507 \pm 1171 ng/mL 11,162 \pm 4617 ng/mL, respectively.

6.4.4. Immunogenicity

The blood sampling scheme for immunogenicity assessment in XLH clinical trials are summarized in **Table 33**.

Table 33. Immunogenicity Sampling Plan in burosumab XLH Clinical Studies

Study	ADA Assessment Time Points
Pediatric Studies	
UX023-CL201	Baseline, Week 16, 24, 36, 56, 64, 88, 112, 136, 160 (ET)/EOSI (and in Amendment 7; EOSII)
UX023-CL205	Baseline, Week 4, 12, 40, (and in Amendment 2; Week 64, 160)
Adult Studies	
KRN23-INT-001	Day 0, D28, D56, D84, D120
KRN23-INT-002	Visits 1, 8, 24, 49 corresponding to Baseline and approximate study days (± 5) 53, 165, 333, 374, 417
UX023-CL203	Baseline, Week 4, 12, 24, 36, 48, 72, 96, 120, 144
UX023-CL303	Screening Visit 2, Week 4, 24, 48, 72, 96/EOSI, EOSII/ET
UX023-CL304	Day 0, Week 4, 24, 48, 72, 96/ET

(Source: Table 2.7.2.4.1.1.1 of Module 2.7.2)

Immunogenicity incidences

The ADA incidences in pediatric XLH studies are summarized in **Table 34**. A total of 4 out of 65 subjects (6.2%) were tested positive for ADA at baseline. No subjects who were negative for ADA at baseline showed positive for ADA after burosumab treatment.

The ADA incidences in adult XLH studies are summarized in

Table 35. A total of 18 out of 176 subjects (10.2%) were tested positive for ADA at baseline. No subjects who were negative for ADAs at baseline showed positive for ADA after burosumab treatment.

Table 34. Anti-drug Antibodies: Multiple-dose Studies in Pediatric XLH

	Baseline Result	Worst Post-Baseline Result	CL201		CL205		Total KRN23 Q2W (N=39) n (%)	Total KRN23 (N=65) n (%)
			KRN23 Q4W* (N=26) n (%)	KRN23 Q2W (N=26) n (%)	Total KRN23 (N=52) n (%)	KRN23 Q2W (N=13) n (%)		
Baseline	Negative		23 (88.46%)	25 (96.15%)	48 (92.31%)	13 (100.00%)	38 (97.44%)	61 (93.85%)
	Positive		3 (11.54%)	1 (3.85%)	4 (7.69%)	0	1 (2.56%)	4 (6.15%)
Post-Baseline	Negative	Negative	23 (88.46%)	25 (96.15%)	48 (92.31%)	13 (100.00%)	38 (97.44%)	61 (93.85%)
	Positive	Negative	3 (11.54%)	1 (3.85%)	4 (7.69%)	0	1 (2.56%)	4 (6.15%)

(Source of data: Table 14.1.3.7.1 of ISS)

Table 35. Anti-drug Antibodies: Multiple-dose Studies in Adult XLH

		CL303							
		Double-Blind Period (Week 0-24)				CL304	CL203	INT-001/002*	
Baseline Result	Worst Post-Baseline Result	Placebo (N=66) n (%)	KRN23 (N=68) n (%)	Total KRN23 (N=134) n (%)	KRN23 (N=14) n (%)	KRN23 (N=20) n (%)	KRN23 (N=28) n (%)	Total KRN23 (N=176) n (%)	
Baseline	Negative	61 (92.42%)	60 (88.24%)	121 (90.30%)	10 (71.43%)	19 (95.00%)	27 (96.43%)	158 (89.77%)	
	Positive	5 (7.58%)	8 (11.76%)	13 (9.70%)	4 (28.57%)	1 (5.00%)	1 (3.57%)	18 (10.23%)	
Post-Baseline	Negative	60 (90.91%)	59 (86.76%)	119 (88.81%)	10 (71.43%)	19 (95.00%)	27 (96.43%)	156 (88.64%)	
	Negative	1 (1.52%)	1 (1.47%)	2 (1.49%)	0	0	0	2 (1.14%)	
	Positive	5 (7.58%)	3 (4.41%)	7 (5.22%)	0	1 (5.00%)	0	8 (4.55%)	
	Positive	0	5 (7.35%)	6 (4.48%)	4 (28.57%)	0	1 (3.57%)	10 (5.68%)	

(Source of data: Table 14.2.3.7.1 of ISS)

Impact of immunogenicity on PK, efficacy and safety

No subjects who were negative for ADA at baseline were tested positive for ADA following burosumab treatment. As there were assay issues, it is not feasible to evaluate the impact of immunogenicity on PK, efficacy, or safety until reanalysis of the samples are done with a better assay. See Outstanding Issues and PMC/PMR recommendations.

6.4.5. Population PK Analysis

The population PK review is comprised of two parts: the first part provides the applicant's analyses and results and the second part provides the FDA Reviewer's assessments of the analyses and results and comments.

Applicant's Population PK Analysis

A population PK analysis was conducted by the applicant to characterize the PK of burosumab administered SC in adult and pediatric patients with XLH. The clinically relevant covariates which may explain the variability of the PK parameters were explored and the individual exposure estimates were computed for the subsequent exposure-response analyses.

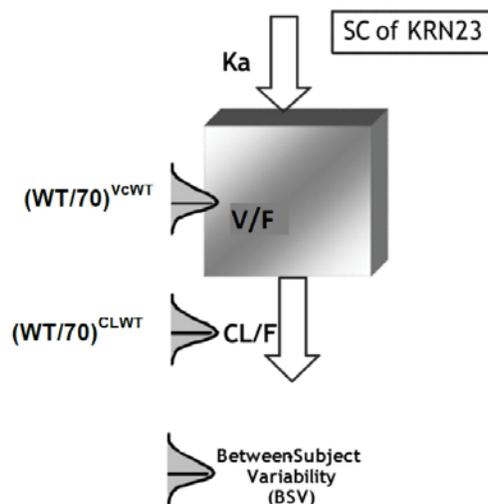
Overall, seven clinical studies were pooled for population PK analysis. These seven studies include four Phase 1/2 studies (KRN23-US-02, KRN23-INT-001, KRN23-INT-002, and UX023-CL203) and one Phase 3 study (UX023-CL303) in adult patients, and two Phase 2 studies in pediatric patients aged 1-4 years (UX023-CL205) and 5-12 years (UX023-CL201).

For PK data in adult patients, burosumab was administered as a single SC dose of 0.1, 0.3, 0.6, or 1.0 mg/kg (N=12); escalating multiple SC doses of 0.05, 0.10, 0.30, and 0.60 mg/kg Q4W (up to 4 doses, N=28); escalating multiple SC doses of 0.30, 0.60, and 1.0 mg/kg Q4W (up to 12 doses, N=22); multiple SC doses of 0.30, 0.60, and 1.0 mg/kg Q4W (up to 36 doses, N=17); or multiple SC doses of 1.0 mg/kg Q4W for 24 weeks (N=68).

For PK data in pediatric patients 5 to 12 years old (N=52), burosumab was administered as multiple SC doses once every 2 weeks (Q2W) or once every 4 weeks (Q4W) for 160 weeks, with a maximum dose level of 2.0 mg/kg Q2W. For PK data in pediatric patients 1 to 4 years old (N=13), burosumab was administered as multiple SC doses of 0.8 mg/kg Q2W for a total of 64 weeks, with a maximum dose level of 1.2 mg/kg Q2W.

A nonlinear mixed effect modeling approach was implemented to characterize the population PK of burosumab using Phoenix NLME 7. A one-compartment PK model with first order absorption from SC injection site and concentration-independent and time-invariant clearance from the serum compartment was selected as the structural model. Body weight based allometric functions on CL/F and V/F was incorporated in the base model. Hypothesis of non-linear clearance of burosumab was evaluated as part of the structural population PK model using Michaelis-Menten equation, but was rejected based on objective function values and model instability. The model schematic and parameters are shown in **Figure 28**.

Figure 28. Schematic Representation of Structural PK Model for Burosumab



KRN23= Burosumab; SC= Subcutaneous; WT=Body weight

Source of data: applicant's Population PK and PK/PD Report ULTR-CSC-105, Figure 4

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The covariates considered for the analysis were age, sex, height, baseline body weight, body mass index, race, ethnicity, country (Japan versus others), study, population (pediatric versus adult patients), product strengths (2, 10, and 30 mg/mL), baseline and time-varying total intact FGF23, baseline albumin, baseline alkaline phosphatase, baseline bone alkaline phosphatase, baseline alanine aminotransferase, baseline creatinine clearance, burosumab dose levels, anti-burosumab antibody, types of phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) mutation, and hyperphosphatemia.

Among all 7 clinical studies (i.e., 5 studies in adults and 2 studies in pediatric patients), the 30 mg/mL strength formulation was used in the majority of burosumab administrations (88%), followed by the 10 mg/mL strength formulation (12%), while the 2 mg/mL strength was used only in Study KRN23-US-02 (0.1%).

Summary statistics of demographic data at baseline for pediatric and adult patients are presented in **Table 36** and **Table 37**, respectively.

Table 36. Summary of Demographic Data at Baseline of Pediatric Patients

Continuous Covariates	Mean (SD) Median [Minimum-Maximum]		
	UX023-CL201 N=52	UX023-CL205 N=13	Overall N=65
Age (years)	8.48 (1.9) 9.00 [5.00-12.0]	2.94 (1.2) 2.80 [1.20-4.90]	7.37 (2.8) 8.00 [1.20-12.0]
Body mass index (kg/m ²)	21.2 (4.2) ^a 20.0 [15.4-33.1]	16.3 (1.6) 15.5 [14.2-20.1]	20.1 (4.3) ^b 18.8 [14.2-33.1]
Height (cm)	119 (11.2) ^a 119 [97.2-144]	89.1 (7.6) 90.2 [77.5-102]	113 (161) ^b 115 [77.5-144]
Weight (kg)	30.5 (9.4) 30.5 [14.7-55.2]	12.9 (1.8) 13.0 [9.20-15.6]	27.0 (11.0) 26.4 [9.20-55.2]
Categorical Covariates	Number of Subjects (% of Total within Study)		
	UX023-CL201 N=52	UX023-CL205 N=13	Overall N=65
Sex			
Female	28 (54%)	4 (31%)	32 (49%)
Male	24 (46%)	9 (69%)	33 (51%)
Race			
White	46 (88%)	12 (92%)	58 (89%)
Black or African American	2 (4%)	1 (8%)	3 (5%)
Others	4 (8%)	0 (0%)	4 (6%)
Ethnic			
Not Hispanic or Latino	50 (96%)	11 (85%)	61 (94%)
Hispanic or Latino	2 (4%)	2 (15%)	4 (6%)
Country			
France	2 (4%)	0 (0%)	2 (3%)
United Kingdom	10 (19%)	0 (0%)	10 (15%)
Netherlands	4 (8%)	0 (0%)	4 (6%)
USA	36 (69%)	13 (100%)	49 (75%)
Dosing Regimens			
Q2W	26 (50%)	13 (100%)	39 (60%)
Q4W	26 (50%)	0 (0%)	26 (40%)
Antibody			
Negative	48 (92%)	12 (92%)	61 (94%)
Positive	4 (8%)	1 (8%)	4 (6%)
PHEX mutation			
Pathogenic or Likely Pathogenic Mutation	46 (88%)	12 (92%)	58 (89%)
Variants of Uncertain Significance	4 (8%)	1 (%)	5 (8%)
Likely Benign or No Mutation	2 (4%)	0 (0%)	2 (3%)

Source of data: applicant's Population PK and PK/PD Report ULTR-CSC-105, Table 11.2.1, 11.2.2.

Table 37. Summary of Demographic Data at Baseline of Adult Patients

Continuous Covariates	Mean (SD) Median [Minimum-Maximum]				
	KRN23-INT-001 N=28	KRN23-US-02 N=12	UX023-CL203 N=17	UX023-CL303 N=80	Overall ^a N=115
Age (years)	41.9 (13.8) 41.5 [19.0-66.0]	47.9 (10.5) 48.5 [25.0-68.0]	50.1 (11.3) 54.0 [25.0-67.0]	40.8 (12.0) 41.5 [20.0-63.4]	41.5 (12.5) 41.6 [19.0-68.0]
Body mass index (kg/m ²)	34.2 (11.0) 31.3 [19.7-68.2]	32.1 (7.30) 31.3 [20.5-48.2]	36.8 (10.9) 35.4 [19.3-52.7]	30.6 (7.45) ^b 30.0 [19.7-64.6]	31.6 (8.4) ^c 30.2 [19.7-68.2]
Height (cm)	150 (12.2) 150 [122-170]	151 (5.81) 150 [143-165]	148 (10.0) 147 [133-171]	153 (9.47) ^b 152 [126-176]	152 (10.0) ^c 151 [122-176]
Weight (kg)	75.8 (20.7) 71.4 [46.4-124.3]	72.9 (16.1) 74.8 [48.1-103]	80.1 (24.4) 75.5 [45.2-126.7]	71.7 (18.9) 68.1 [37.1-140]	72.7 (18.9) 70.2 [37.1-139.6]
Categorical Covariates	Number of Subjects (% of Total within Study)				
	KRN23-INT-001 N=28	KRN23-US-02 N=12	UX023-CL203 N=17	UX023-CL303 N=80	Overall ^a N=115
Sex					
Female	19 (68%)	6 (50%)	12 (71%)	51 (64%)	72 (63%)
Male	9 (32%)	6 (50%)	5 (29%)	29 (36%)	43 (37%)
Race					
White	27 (96%)	12 (100%)	17 (100%)	66 (83%)	100 (87%)
Black or African American	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Asian	0 (0%)	0 (0%)	0 (0%)	13 (16%)	13 (11%)
Others	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Ethnic					
Not Hispanic or Latino	25 (89%)	0 (0%)	16 (94%)	71 (89%)	91 (79%)
Hispanic or Latino	2 (7%)	0 (0%)	1 (6%)	9 (11%)	11 (10%)
Unknown	1 (4%)	12 (100%)	0 (0%)	0 (0%)	13 (11%)
Country					
Canada	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
France	0 (0%)	0 (0%)	0 (0%)	15 (19%)	15 (13%)
United Kingdom	0 (0%)	0 (0%)	0 (0%)	6 (8%)	6 (5.2%)
Ireland	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0.9%)
Italy	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0.9%)
Japan	0 (0%)	0 (0%)	0 (0%)	7 (9%)	7 (6%)
Korea	0 (0%)	0 (0%)	0 (0%)	4 (5%)	4 (3%)
United States	27 (96%)	12 (100%)	17 (100%)	46 (58%)	80 (70%)
Antibody					
Negative	27 (96%)	12 (100%)	15 (88%)	47 (59%)	95 (83%)
Positive	1 (4%)	0 (0%)	2 (12%)	33 (41%)	20 (17%)
PHEX Mutation					
Pathogenic or Likely Pathogenic Mutation	17 (61%)	1 (8%)	14 (82%)	62 (77%)	78 (68%)
Variants of Uncertain Significance	1 (4%)	0 (0%)	1 (6%)	10 (13%)	11 (10%)
Likely Benign or No Mutation	3 (11%)	3 (25%)	2 (12%)	7 (9%)	10 (9%)
No Available	7 (25%)	8 (67%)	0 (0%)	1 (1%)	16 (14%)

Source of data: applicant's Population PK and PK/PD Report ULTR-CSC-105, Table 11.2.4, 11.2.5

Summary statistics of serum chemistry analytes at baseline for pediatric and adult patients are presented in **Table 38** and **Table 39**, respectively.

Table 38. Summary Statistics of Bone/Serum Chemistry Analytes at Baseline in Pediatric Patients Aged 1 to 12 Years by Clinical Study

Serum Chemistry Analytes	Mean (SD) Median [Minimum-Maximum]		
	UX023-CL201 N=52	UX023-CL205 N=13	Overall N=65
Bone alkaline phosphatase (µg/L)	157 (51.3) 152 [60.0-264]	176 (95.3) 165 [13.0-396]	161 (62.1) 155 [13.0-396]
Serum albumin (g/dL)	4.40 (0.263) 4.40 [3.80-5.30]	4.56 (0.218) 4.60 [4.10-4.90]	4.44 (0.261) 4.40 [3.80-5.30]
Serum alkaline phosphatase (U/L)	459 (105) 468 [237-706]	548 (194) 506 [286-980]	477 (131) 468 [237-980]
Serum alanine aminotransferase (U/L)	15.4 (4.50) 15.0 [7.00-27.0]	17.9 (4.35) 17.0 [13.0-27.0]	15.9 (4.56) 15.0 [7.00-27.0]
Creatinine clearance (mL/min/1.73m ²)	160 (32.7) ^a 159 [100-226]	198 (87.8) 175 [124-469]	168 (50.9) ^b 164 [100-469]
Serum total FGF23 (pg/mL)	157 (93.6) 127 [33.0-445]	417 (402) 283 [81.7-1300]	209 (220) 133 [33.0-1300]
Serum phosphorus (mg/dL)	2.33 (0.356) 2.20 [1.80-3.50]	2.51 (0.284) 2.50 [2.00-2.90]	2.36 (0.348) 2.30 [1.80-3.50]

Source of data: applicant's Population PK and PK/PD Report ULTR-CSC-105, Table 11.2.3.

Table 39. Summary Statistics of Bone/Serum Chemistry Analytes at Baseline in Adult Patients by Clinical Study

Chemistry Analytes	Mean (SD) Median [Minimum-Maximum]				
	KRN23-INT-001 N=28	KRN23-US-02 N=12	UX023-CL203 N=17	UX023-CL303 N=80	Overall ^a N=115
Bone alkaline phosphatase (µg/L)	28.1 (12.6) 25.5 [8.20-52.4]	29.9 (12.4) 28.8 [15.5-60.8]	31.6 (19.0) 25.6 [12.3-79.1]	26.2 (27.9) 17.0 [5.00-212]	27.0 (24.2) 19.0 [5.00-212]
Serum albumin (g/dL)	4.34 (0.319) 4.30 [3.90-5.20]	4.01 (0.332) 3.85 [3.60-4.70]	4.47 (0.220) 4.50 [4.10-4.90]	4.37 (0.245) 4.35 [3.90-5.30]	4.33 (0.296) 4.30 [3.60-5.30]
Serum alkaline phosphatase (U/L)	124 (38.5) 113 [56.0-201]	116 (26.9) 111 [78.0-163]	130 (50.8) 122 [57.0-253]	123 (58.2) 115 [26.0-338]	122 (52.1) 113 [26.0-338]
Serum alanine aminotransferase (U/L)	27.0 (22.5) 20.0 [9.00-92.0]	22.7 (5.50) 23.0 [14.0-32.0]	33.6 (25.1) 25.0 [11.0-109]	26.1 (17.3) 20.0 [7.00-91.0]	26.1 (18.1) 20.0 [7.00-92]
Creatinine clearance (mL/min)	147 (64.2) 135 [64.3-355]	128 (53.5) 113 [49.9-248]	130 (67.5) 111 [66.1-349]	148 (64.1) 129 [66.4-387]	147.0 (63.5) 130 [49.9-387]
Serum total FGF23 (pg/mL)	94.8 (92.4) ^b 67.1 [15.0-344]	109 (56.7) 88.4 [38.3-208]	295 (232) 198 [99.2-946]	142 (285) ^c 79.7 [15.0-2270]	130 (242) ^d 79.2 [15.0-2270]
Serum phosphorus (mg/dL)	1.89 (0.326) 1.90 [1.20-2.80]	1.93 (0.454) 1.95 [1.10-2.60]	1.92 (0.319) 1.90 [1.30-2.60]	2.01 (0.327) 2.02 [1.24-3.10]	1.96 (0.343) 1.90 [1.10-3.10]

Source of data: applicant's Population PK and PK/PD Report ULTR-CSC-105, Table 11.2.6.

The population PK dataset contained 2262 serum concentrations of burosumab from 180 patients with XLH, including 65 pediatric patients (aged from 1 to 12 years old with median body weight of 26.4 kg) and 115 adult patients (aged from 19 to 68 years old with median body weight of 70.2 kg). Among the PK data, 644 serum burosumab concentrations were collected from pediatric patients and 1618 concentrations were from adult patients.

Stepwise forward addition and backward elimination approach was used during the PK covariate analysis process. After incorporating allometric functions of body weight on CL/F and on V/F in the structural model, no additional significant covariates were identified in the final population PK model.

The population mean parameter estimates (based on a 70-kg adult XLH patient) and their associated precision for the final population PK model are presented in **Table 40**. The diagnostic plots and visual predictive check (VPC) plots are presented in **Figure 29** and **Figure 30**, respectively.

Table 40. Parameter Estimates for the Final Population PK Model

	Parameters	Typical Values (RSE%)	BSV	IOV
PK Parameters	Ka (day ⁻¹)	0.380 (7.18)	0 (fixed)	
	V/F (L)	8.027 (2.81)	25.3%	23.3%
	CL/F (L/day)	0.290 (3.23)	29.5%	12.7%
Covariate on CL/F	(WT/70) ^{effect}	0.893 (4.43)		
Covariate on V/F	(WT/70) ^{effect}	1 FIX		
Residual errors	Proportional error (%)	20.2 (3.60)		

BSV= Between-subject variability; IOV= Inter-occasion variability; RSE = Relative standard error; WT= Body weight (kg)

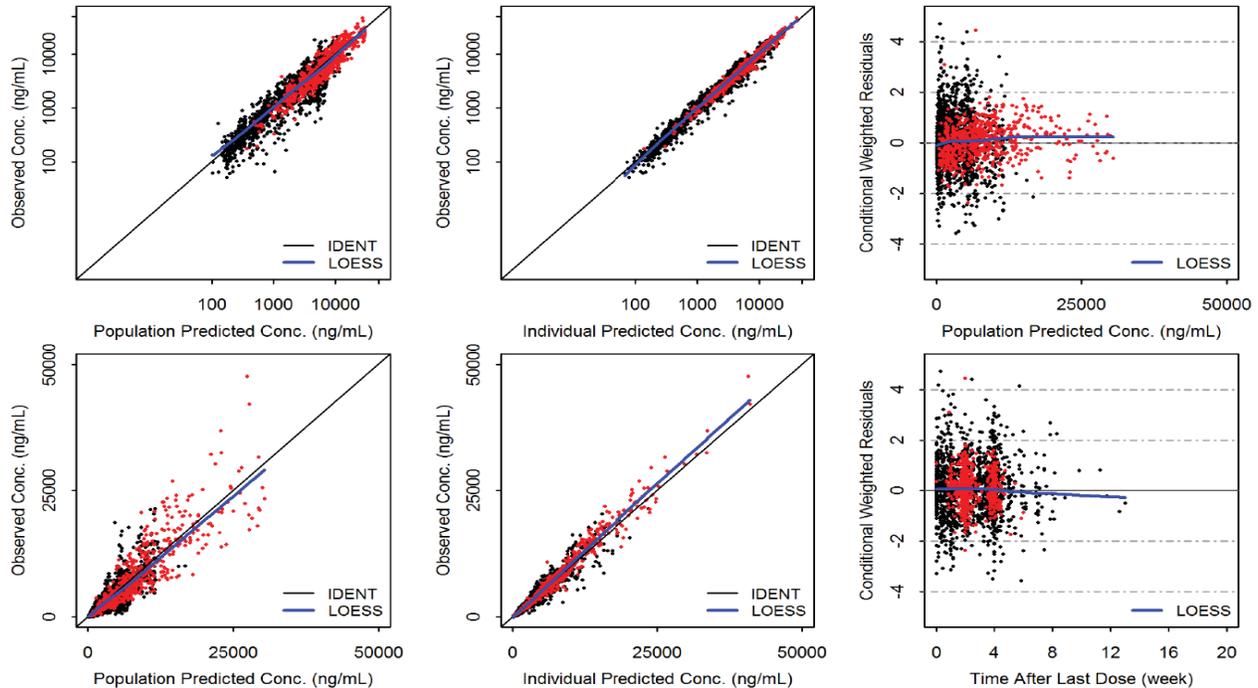
Shrinkage: CL/F: 22.0%; V/F: 39.5%

Correlation between CL/F and V/F was 0.445.

Note: Inter-occasion term based on enrolled study was added in the model to be able to estimate a separate set of PK parameters within each study.

Source of data: applicant's Population PK and PK/PD Report ULTR-CSC-105, Table 8.

Figure 29. Goodness of Fit Plot for the Final Population PK Model

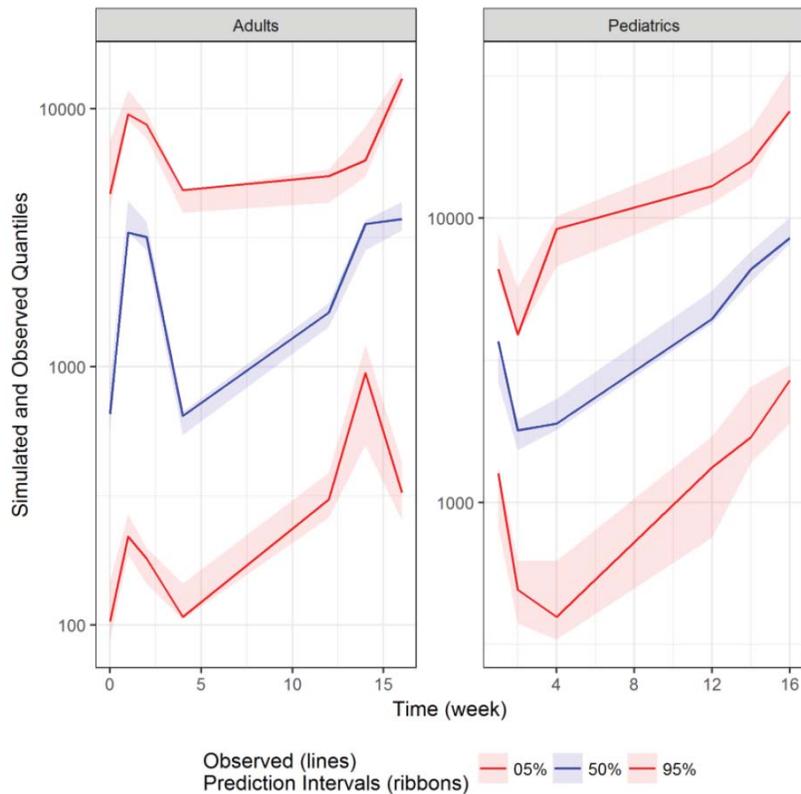


Red dots: Pediatric data; Black dots: Adult data

IDENT= Line of identity; LOESS = Locally weighted scatter plot smoothing

Source of data: applicant's Population PK and PK/PD Report ULTR-CSC-105, Figure 7

Figure 30. Visual Predictive Check for the Final Population PK Model for Adults and Pediatric Patients



Note: Full lines represent percentiles of observed burosumab concentrations within each bin (50th percentiles are in blue and 5th and 95th percentiles in red); shaded areas represent 95% percentile interval of percentiles of predicted concentrations (50th percentiles are in blue and 5th and 95th percentiles in red).

Source of data: Applicant's Population PK and PK/PD Report ULTR-CSC-105, Figure 8

The final population PK model was used to simulate individual exposure parameters (C_{avg} , C_{max} , C_{min} , and AUC) of burosumab at steady state with Q2W dosing for pediatric patients and Q4W dosing for adult patients. Descriptive statistics of burosumab exposure parameters by study are presented in **Table 41**.

Table 41. Descriptive Statistics of PK Exposure Levels of Burosumab under Steady-State in Pediatric and Adult Patients with XLH based on Their Last Dose Levels

PK Exposure	Mean (CV%) Median [Minimum-Maximum]					
	UX023- CL201 N=52	UX023- CL205 N=13	KRN23- INT-001 N=28	KRN23- INT-002 N=22	UX023- CL203 N=20	UX023- CL303 N=134
C _{min} (ng/mL)	15775(45%) 15732[4808-40503]	12028(31%) 10657[7409-19167]	2256(52%) 2082[500-4414]	4058(43%) 3950[1526-7139]	4157(36%) 4173[1538-6922]	5711(48%) 5265[1351-16185]
C _{avg} (ng/mL)	19185(43%) 18818[6613-46550]	14580(29%) 12844[9155-23494]	3863(43%) 3491[658-6372]	6879(37%) 6436[2719-12250]	6623(31%) 6764[2468-9796]	8631(37%) 8416[2763-20569]
C _{max} (ng/mL)	21349(42%) 20935[7249-50283]	16195(28%) 14419[10265-26235]	5301(42%) 5246[728-9815]	9363(36%) 8915[3465-16684]	8723(30%) 8818[3254-12390]	11114(34%) 10955[3405-23918]
AUC (µg × day/mL)	269(43%) 263[92.6-652]	204(29%) 180[128-329]	108(43%) 97.7[18.4-178]	193(37%) 180[76.1-343]	185(31%) 189[69.1-274]	242(37%) 236[77.4-576]
Last dose (mg)	38.9(47%) 39.0[15.0-90.0]	11.8(19%) 12.0[9.00-18.0]	35.8(52%) 35.6[2.32-77.5]	66.0(47%) 63.6[17.3-133]	60.8(51%) 57.0[18.0-120]	66.4(28%) 69.0[8.10-90.0]

Note: Patients in KRN23-US-02 received a single dose only and thus were not retained for the simulations.

Source of data: Applicant's Population PK and PK/PD Report ULTR-CSC-105, Table 10.

Reviewer Comments:

The reviewer found that the applicant's population PK model reasonably described the PK characteristics of burosumab which showed <30% between-subject variability in parameter estimates and a proportional residual error of 20%. Visual inspection indicates that the model is predictive over the range of concentrations observed in the clinical studies.

6.4.6. Exposure-response analyses

Applicant's analysis

Exposure-response (ER) analysis for efficacy has been conducted by applicant for serum phosphorus change from baseline using a PK/PD model based on pooled data from five adult studies (KRN23-US-02, KRN23-INT-001, KRN23-INT002, UX023-CL203, and UX023-CL303) and two pediatric studies (UX023-CL201 and UX023-CL205). The effects of age on the key PK/PD parameters (e.g., E₀, E_{max} and EC₅₀) were evaluated. A total of 161 adult patients and 65 pediatric patients were included in the ER analysis with a starting dose of 0.1 to 1.0 mg/kg. There were a significant number of serum phosphorus concentrations with no paired burosumab concentration data; therefore, serum burosumab concentrations were simulated based on final population PK model of serum burosumab at the corresponding PD timepoint were used for ER analysis.

It has been established based on intensive PK/PD data in Study KRN23-US-02 that the PK and PD relationship of serum burosumab is directly linked without discernible temporal delay following SC administration (**Figure 14**). Therefore, indirect PK/PD models were not explored. However, it should be noted that a delay in increase in serum phosphorus levels as burosumab concentration increased was observed following a single IV dose administration.

The PK/PD relationship was explored using an E_{max} model, as shown below.

$$\text{Phosp} = E_0 + (\text{sim}C_{\text{burosumab}}^\gamma \cdot E_{\text{max}}) / (EC_{50}^\gamma + \text{sim}C_{\text{burosumab}}^\gamma)$$

Where Phosp is the serum phosphorus levels; simC_{burosumab} is the individual predicted burosumab concentrations; EC₅₀ is the serum burosumab concentration to reach 50% of maximal effect; E_{max} is the maximum effect and γ is the Hill coefficient.

Reviewer Comments:

The observed PK/PD relationship following SC administration should not be interpreted as evidence for direct response given the observed delay in PD response following a single IV dose administration. However, the PK/PD modeling approach using empirical Emax model is acceptable for the purpose to describe the PK/PD data following SC administration.

Covariate analysis showed that body weight was a significant covariate on E₀ and E_{max}. The effects of age (1.2-68 years) on the key PK/PD parameters, E₀, E_{max} and EC₅₀, were also evaluated; however, after incorporating the effect of body weight on E₀ and E_{max} in the structural model, age had no additional significant effect on these two parameters and thus was not retained in the model. No other covariate including sex (female (N=32) and male

(N=33)), race (White (N=58), Black or African American (N=3), and others (N=4)), ethnicity [Hispanic or Latino (N=4); and not Hispanic/Latino (N=61)], height (77.5-176 cm), PHEX mutation (pathological and likely pathological PHEX mutation (N=58), variants of uncertain significance (VUS) (N=5), and likely benign and no PHEX mutation (N=2)), and baseline total FGF23 (15-2270 pg/mL) was identified although the number of non-white subjects was small.

Estimates for the typical population values of PK/PD parameters are presented in **Table 42**. The typical values of E_{max} and EC_{50} were 1.92 [mg/dL]/[ng/mL] and 5783.2 ng/mL, respectively. A statistically significant negative correlation was observed between serum phosphorus at baseline and WT, with estimated point estimate of -0.13. A statistically significant positive correlation was observed between maximum effect of burosumab treatment and WT. This modeling result suggests there may be a decreased risk of hyperphosphatemia in pediatric patients as compared to adult patients. Large parameter shrinkages were associated with separate BSV estimates for the two populations, indicating that the available PK/PD data may not be adequate to support simultaneous estimation of BSV for pediatric and adult populations with good precision.

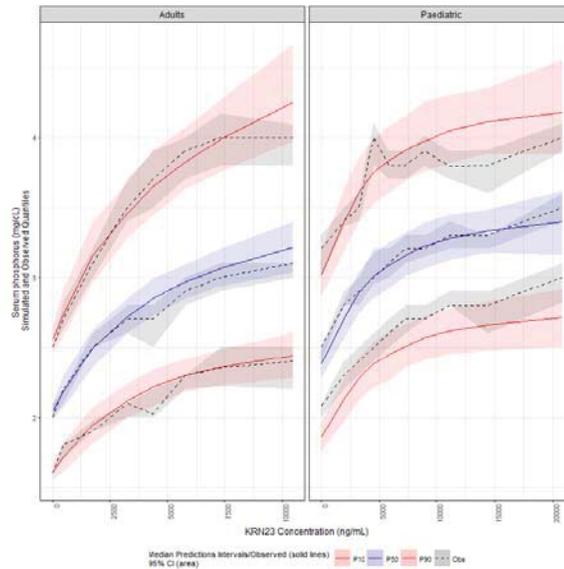
Table 42. Population PK/PD Parameters in Pooled Data in Pediatric and Adult XLH Populations

Parameters		Modified PK/PD Model		
		Typical Values	BSV	Shrinkage
PD Parameters	E_0 (mg/dL)	2.05 (1.09%)	12.3%	11.2%
	EC_{50} (ng/mL)	3331.7 (14.6%)	137% for adults	43.9%
			73.0% for pediatrics	65.7%
	Γ_{max}	1.24 (8.56%)		
E_{max} ([mg/dL]/[ng/mL])	1.56 (8.27%)	70.1% for adults	36.7%	
		25.4 for pediatrics	64.1%	
Covariate on E_0	$(WT/70)^{effect}$	-0.13 (11.6%)		
Covariate on E_{max}	$(WT/70)^{effect}$	0.29 (23.8%)		
Error Model		Proportional error (%) 12.6%		

Source of data: Applicant's response to IR on Nov 10th, 2017, Page 4, Table 1

Figure 31 displays the Visual Predictive Check (VPC) plots stratified by adult and pediatric subjects. Overall, the model reasonably predicted the PK/PD relationship of burosumab for majority of data.

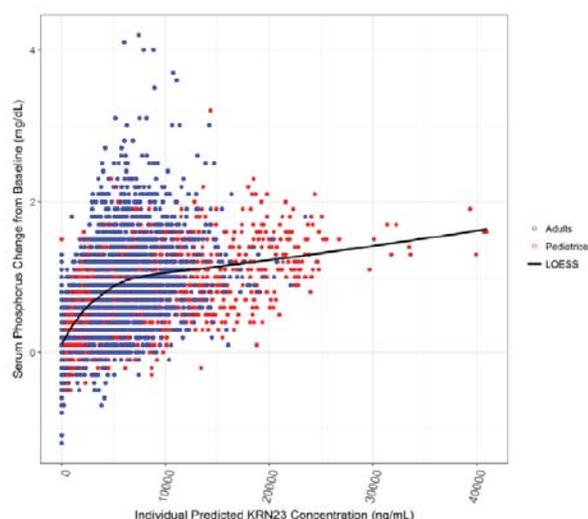
Figure 31. VPC Plots of Serum Phosphorus Levels in Pooled Data in Pediatric and Adult Subjects with XLH



Source of data: Applicant's response to IR on Nov 10th, 2017, Page 5, Figure 2

The ER relationship between individual predicted burosumab concentrations and the serum phosphorus change from baseline based on pooled data in pediatric and adult XLH populations are shown in **Figure 32**.

Figure 32 Relationship between Serum Phosphorus Change from Baseline and Individual Predicted Concentrations of Burosumab in Adult and Pediatric Subjects with XLH



Source of data: Applicant's study report for population PK and ER analysis (Report 105), Page 53, Figure 12

Reviewer Comments:

Although results from PK/PD modeling using the pooled data from adults and pediatrics population suggested age is not a significant covariate in the PK/PD relationship after including weight as covariate, there is still uncertainty about the effect of age on PK/PD relationship as weight and age is highly correlated in pediatric population. The Reviewer conducted an independent analysis to explore the relationship between burosumab concentrations and serum phosphorus change from baseline, a similar result was found (**Figure 19**) that the PK/PD relationship appeared to be slightly different between pediatrics and adults. Therefore, additional PK/PD analyses were conducted for the pediatric and adult populations separately as sensitivity analysis to evaluate whether the PK/PD parameters are similar between the two populations.

Table 43 summarizes the typical population PK/PD parameters estimated from the pediatric and adult datasets, respectively. The estimated typical value of E₀ for pediatric subjects (2.46 mg/dL) was 22% higher than that in adult subjects (2.02 mg/dL), which is consistent with the observed data. The typical value of EC₅₀ derived with pediatric data (9580 ng/mL) was much higher than that derived with the adult data (2574 ng/mL), and accompanied with higher estimated E_{max} values in the pediatric population (1.69 vs. 1.35 mg/dL). Noteworthy, the between-subject variability (BSV) and parameter shrinkage for EC₅₀ were large in the adults and

could not be estimated for the pediatrics. This, taken together with large BSV associated with the effort to estimate separate EC50 values in adult and pediatric populations using the pooled dataset (**Table 42**), suggests that the current PK/PD dataset may not adequately support such independent analysis in the two sub-populations. In other words, the results from subgroup population PK/PD analysis should be interpreted carefully.

Table 43. Population PK/PD Parameters Derived Independently from Pediatric and Adult Subjects

Parameters		Pediatric Population (MODEL P10)			Adult Population (MODEL A8)		
		Typical Values	BSV	Shrinkage	Typical Values	BSV	Shrinkage
PD Parameters	E0 (mg/dL)	2.46 (1.68%)	10.9%	12.0%	2.02 (12.8%)	12.1%	12.5%
	EC ₅₀ (ng/mL)	9580 (25.4%)			2574 (10.5%)	80.3%	36.5%
	G _{am} (Hill term)	0.85 (11.1%)	39.5%	35.1%	1.43 (1.10%)		
	E _{max} ([mg/dL]/[ng/mL])	1.69 (11.0%)	31.4%	16.0%	1.35 (6.97%)	54.0%	22.5%
Error Model		Prop error: 15.6% Add error: 0.046 mg/dL			Prop error: 13.7%		

Source of data: Applicant's response to IR on Nov 10th, 2017, Page 6, Table 2

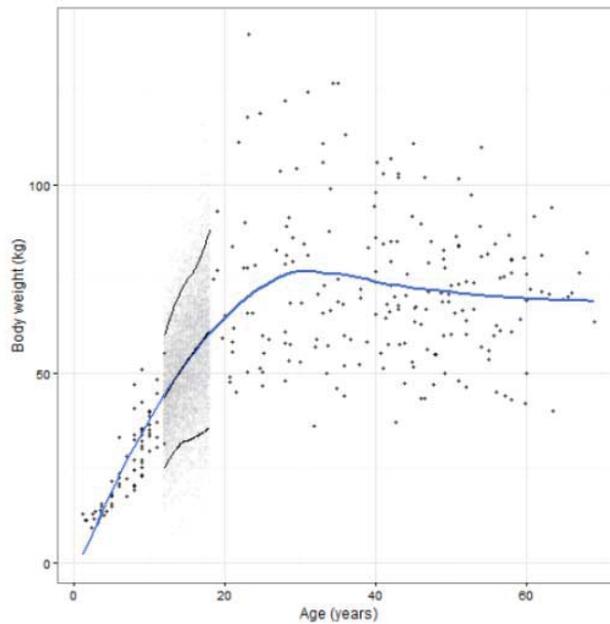
Figure 19 represent the VPC plots of the population PK/PD model derived from pediatric-only data and adult-only data. The E_{max} model can well describe the ER relationship for adult subjects but show a little bit over prediction for upper bound in pediatric subjects.

In order to incorporate body weight of adolescent into PK/PD simulations, the body weight of subjects with XLH was modeled using generalized additive models for location scale and shape (GAMLSS) based on body weight distribution observed in pediatric subjects (1- <12 years old) and adult subjects (18 - <69 years old) with XLH. The distribution of WT in adolescent patients with XLH was predicted based on the GAMLSS model and is presented in **Figure 33**. The predicted mean and median values of body weight in the adolescent population were 53.3 and 53.2 kg and 52.7 and 53.0 kg, respectively and the range were [22.7-87.7] kg and [22.7-89.3], respectively.

Reviewer Comments:

The predicted body weight range for adolescent patients (12-17 years old) by applicant was consistent with CDC growth chart, which was 30.5 to 90.4 kg based on the percentile of 5% and 95% for subjects aged 12 years and 17.99 years, respectively. However, it should be noted that the predicted body weight range may not reflect the real body weight range in adolescent patients with XLH, and may affect the accuracy and precision of further PK/PD prediction.

Figure 33. Distribution of Body Weight in Subjects with XLH



Source of data: Applicant's study report for population PK and ER analysis (Report 105), Page 61, Figure 16

The predicted body weight of adolescent was used to simulate the concentrations of burosumab by population PK model and the simulated burosumab concentrations at steady state is presented in **Table 44**.

Table 44. Predicted Burosumab Concentrations at Steady State in XLH Adolescent Subjects (Dose Levels Rounded to the Nearest 10 mg with Maximum of 90 mg)

Analyte	PK Exposure	Geometric Mean (Geometric CV%) Median [5 th -95 th percentiles]	
		0.8 mg/kg Q2W	1.0 mg/kg Q4W
Serum KRN23	C _{min} (ng/mL)	8959 (14%) 9691 [1085-58733]	3710 (21%) 5058 [203-31180]
	C _{avg} (ng/mL)	12344 (11%) 12388 [2258-66180]	8361 (11%) 8781 [1634-38011]
	C _{max} (ng/mL)	14329 (10%) 14287 [2961-69062]	11857 (9%) 12057 [2752-48641]

Source of data: Applicant's study report for population PK and ER analysis (Report 105), Page 64, Table 15

Reviewer Comments:

The predicted PK exposure in adolescents with a dose of 0.8 mg/kg Q2W was similar to those in pediatric patients aged 1 to 12 years at the same dose and the predicted PK exposure in adolescents with a dose of 1.0 mg/kg Q4W was similar to those in adult patients at the same dose, which may be due to the model relying on dosing based on body weight.

The predicted burosumab concentrations were used to simulate the serum phosphorus concentrations by the population PK/PD model developed with pediatric only data to support dosing regimens of burosumab in adolescent population with XLH. The simulation results are presented in **Figure 20** which display the steady-state serum phosphorus time profiles following burosumab treatments in adolescent subjects with XLH receiving 0.8 mg/kg Q2W and 1.0 mg/kg Q4W dose regimens, respectively.

Simulated serum phosphorus and serum phosphorus change from baseline are presented in **Table 45**.

Table 45. Descriptive Statistics of Predicted PD in XLH Adolescent Subjects (Dose Levels Rounded to the Nearest 10 mg with Maximum of 90 mg)

Analyte	PD Exposure	Geometric Mean (Geometric CV%) Median [5th-95th percentiles]	
		0.8 mg/kg Q2W	1.0 mg/kg Q4W
Serum Phosphorus	C _{min} (mg/dL)	3.36(17%) 3.30[2.53-4.38]	3.14(18%) 3.09[2.38-4.12]
	C _{avg} (mg/dL)	3.45(16%) 3.38[2.65-4.46]	3.31(16%) 3.26[2.55-4.24]
	C _{max} (mg/dL)	3.50(16%) 3.43[2.73-4.52]	3.44(16%) 3.40[2.70-4.42]
Serum Phosphorus Change from Baseline	C _{min} (mg/dL)	0.882(56%) 0.816[0.168-1.73]	0.667(73%) 0.596[0.0369-1.60]
	C _{avg} (mg/dL)	0.972(49%) 0.896[0.317-1.80]	0.833(56%) 0.753[0.239-1.72]
	C _{max} (mg/dL)	1.03(46%) 0.952[0.387-1.88]	0.971(49%) 0.884[0.373-1.88]

Source of data: Applicant's response to IR on Nov 10th, 2017, Page 9, Table 3

Difference in burosumab concentrations between the dosing regimens do not translate into difference in serum phosphorus levels. For both dose regimens, the range of projected serum phosphorus levels [min-max] were compared to the normal serum phosphorus range referenced for pediatrics (3.2-6.1 mg/dL), which was the targeted serum phosphorus range for burosumab therapy in the burosumab clinical studies from both safety and efficacy considerations. For the 0.8 mg/kg Q2W and 1.0 mg/kg Q4W dosing regimens, approximately 42% and 58% of the simulated minimum of serum phosphorus levels were lower than 3.2 mg/dL (the lower bound of normal serum phosphate range), respectively, whereas 1.6% and 1.0% of the simulated maximum of serum phosphorus levels were higher than 5.0 mg/dL, respectively. Since the 0.8 mg/kg Q2W dosing regimen is predicted to afford a higher probability for patients to achieve at least 3.2 mg/dL serum phosphate (lower bound of normal range), it may be recommended that the adolescent XLH patients should receive the same dose as younger pediatric patients (1-12 years old).

Rationale for selection of the starting dose in adolescent

The proposed starting dose of 0.8 mg/kg Q2W for adolescent patients is acceptable for the following reasons: 1) In Study CL205 the proposed 0.8 mg/kg Q2W as starting dose with titration to target normal serum phosphorus level provided a favorable risk/benefit profile in pediatric patients (1-12 years). 2) the PK exposure in adolescent patients following 0.8 mg/kg

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Q2W is predicted to be similar to that in pediatric patients (1-12 years old) based on the popPK analysis. 3) The results from PK/PD modeling and simulation indicated that a starting dose of 0.8 mg/kg Q2W would provide more favorable risk/benefit profile than 1 mg/kg Q4 W in adolescents patients. Although PK/PD modeling analysis suggested that there is still uncertainty in PK/PD characteristics in pediatrics patients due to the limitation of the data, dose will be individually titrated to achieve normal serum phosphorus concentration to warrant optimal individualized dose for both efficacy and safety. Overall, the proposed starting dose of 0.8 mg/kg Q2W for all pediatric patients (<18 years old) is acceptable as it appears to represent a more conservative approach.

7. Sources of Clinical Data and Review Strategy

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7.1.1. Table of Clinical Studies

The following table lists all repeat-dose studies of burosumab in patients with XLH, and a historical control study also submitted to the BLA. Other burosumab studies not included in this table are: (b) (4)

Table 46 Listing of clinical trials relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Pediatric uncontrolled studies to support efficacy and safety</i>								
UX023- CL201	0216 3577	Phase 2 Open label Randomized to dosing interval Dose titration	Burosumab SC Q2W or Q4W Doses 0.1 to 2.0 mg/kg	Rickets by xray PD-serum phos, ALP Growth, deformities Physical function, pain PK, safety	Week 64 data in BLA, ongoing extension	52	Children age 5-12 y/o with XLH	9 centers: US (4) UK (3) France (1) Netherlands (1)
UX023- CL205	0275 0618	Phase 2 Open label Single arm	Burosumab SC Q2W Dose: 0.8 – 1.2 mg/kg	Safety, PK PD-serum phos, ALP Rickets by xray Growth, deformities Physical function, PK	Week 24 data in BLA, ongoing extension	13	Children age 1-5 y/o with XLH	3 centers in US
UX023- CL002	N/A	Retrospective historical study of pediatric XLH	N/A (patients were receiving conventional therapy)	Rickets by xray Growth PD-serum phos, ALP	N/A	52 (100 planned)	Children age 5-14 y/o with XLH	2 centers in US, 1 in Canada
<i>Adult controlled study to support efficacy and safety</i>								
UX023- CL303	0252 6160	Phase 3 Randomized Double blind Placebo control	Burosumab SC 1.0 mg/kg Q4W vs. placebo (1:1)	PD-serum phos Pain (BPI Q3) Physical function and stiffness (WOMAC) Pseudofracture, fracture	Week 24 and 40 reports in BLA, ongoing extension	134 (Burosumab 68, Placebo 66)	Adults 18-65 y/o with XLH and pain (≥4/10 on BPI-Q3)	25 centers in US, Europe, Japan, S. Korea

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Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Adult uncontrolled study to support efficacy and safety								
UX023- CL304	0253 7431	Phase 3 Open label Single arm	Burosumab SC 1.0 mg/kg Q4W	Osteomalacia (bone biopsy) PD – serum phos	48 weeks, ongoing, limite interim data in BLA	14	Adults 18-65 y/o with XLH	US, Europe, Japan
Other studies pertinent to the review of efficacy or safety								
KRN23- INT-001	0134 0482	Phase 1/2 Open label Intra-subject dose escalation	Burosumab SC Repeat dose Q4W: 0.05, 0.1, 0.3, 0.6 mg/kg	PD-serum phos Additional PD, PK Safety	4 doses – 16 weeks	28 buros 1 placebo	Adults ≥18 y/o with XLH	5 centers in US, 1 in Canada
KRN23- INT-002	0157 1596	Phase 1/2 Open label extension of study INT-001	Burosumab SC Repeat dose Q4W: 0.05, 0.1, 0.3, 0.6, 1.0 mg/kg	PD-serum phos Safety	12 doses – 48 weeks	22 buros 1 placebo	Adults ≥18 y/o with XLH	5 centers in US, 1 in Canada
UX023- CL203	0231 2687	Phase 2 Open label Long term extension of INT-001 and INT-002	Burosumab SC Q4W, continue previous dose from INT-002	PD – serum phos and other markers Safety, immunogenicity	Week 48 CSR in BLA, ongoing extension	20 buros	Adults ≥18 y/o with XLH	5 centers in US

7.1.2. Review Strategy

The pediatric efficacy and safety of burosumab are evaluated in open label studies of children with XLH age 5-12 years (study CL201) and age 1-4 years (study CL205). Adult efficacy and safety are evaluated in a placebo-controlled study (CL303) and an open label bone biopsy study (CL304). Each of these studies is reviewed in detail in section 8 of this review, although only partial interim data are available from CL304. This section represents the combined evaluation of clinical and statistical reviewers.

The remaining repeat-dose studies listed in the above table (studies INT-001/002 and CL203) are not discussed in this section; although these studies provide relevant safety data (which is included in section 8.3 of this review), they do not contribute substantially to the evaluation of efficacy.

The historical control study (CL-002), which provides data on children with XLH-rickets receiving conventional therapy, is described in section 8.1.3 while the key comparison with study CL-201 efficacy data is presented in section 8.2.1.

Data Source

The sources of data used for the evaluation of the efficacy and safety of burosumab for the proposed indication included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references. This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) format are located in the following network path:

- <\\cdsesub5\EVSPROD\BLA761068\0001\m5\datasets>
- <\\cdsesub5\EVSPROD\BLA761068\0017\m5\datasets>

Data and Analysis Quality

Upon further clarification from the applicant to FDA information requests, the statistical reviewer was able to reproduce the analysis results using the submitted analysis datasets.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study UX023-CL201

Study title: 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)

Overview and Objective

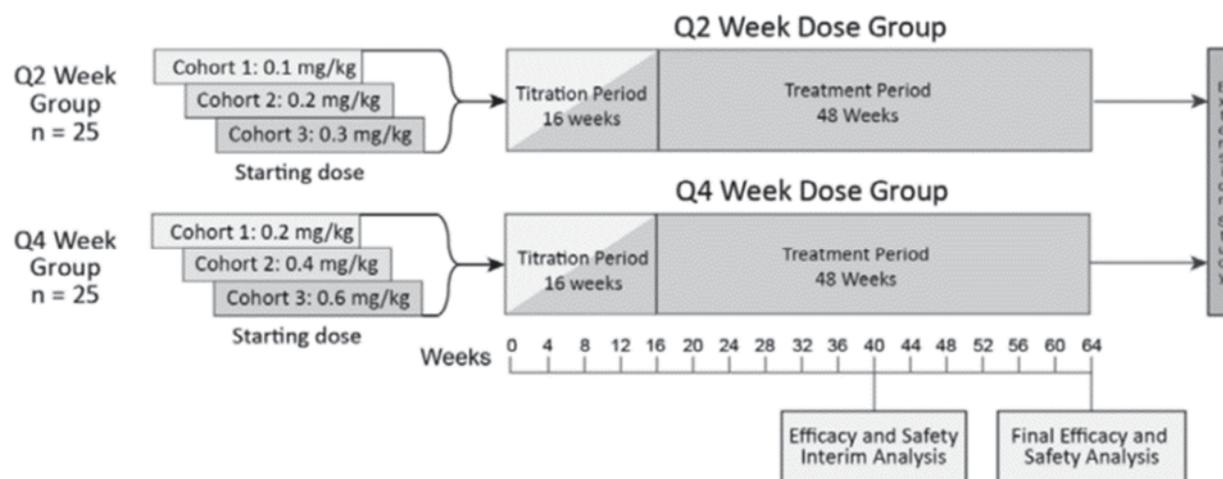
The objectives of study CL201 are to identify, in pediatric XLH patients age 5-12 years old, a burosumab regimen (dose and interval) based on safety and pharmacodynamic (PD) effects, primarily serum phosphorus, and to obtain a preliminary assessment of the effects of burosumab on bone health and other clinical outcomes. The study is ongoing and, by agreement with the Division, the week 64 study report is included in the BLA.

Study Design

This is a randomized, open label, dose-finding study conducted at 9 centers in the US and Europe. Patients were assigned sequentially to one of three cohorts, with starting doses of 0.2, 0.4 or 0.6 mg/kg per month and staggered enrollment (figure below). Within each of the 3 cohorts, patients were randomized (1:1, stratified by sex) to once every 2 weeks (Q2W) or once every 4 weeks (Q4W) dosing; the dosing interval was the primary comparison of interest, while the actual doses were titrated. There was no control group.

The study was originally planned to enroll approximately 30 patients or 10 for each cohort. Protocol amendment 3 expanded cohort 3 from 10 to 30 patients, so the total study enrollment increased to 50 patients. The 1:1 randomization for Q2W versus Q4W dosing continued in this “expansion” cohort of approximately 20 patients.

Figure 34 Study CL201 Schema



After the first dose, individual doses were adjusted monthly based on fasting serum phosphorus at 14 days post-dose, which represents a pre-dose level for the Q2W group, and a midpoint (approximately peak) level for the Q4W group. For both groups, the target for serum phosphorus was initially set at 3.5-4.5 mg/dL, considered to approximate the lower half of the age-specific reference range (estimated at 3.2-6.1 mg/dL). It was predicted that achieving this target would restore bone mineralization and growth plate function, while minimizing the risk of hyperphosphatemia or ectopic calcification. Based on initial data, the target range was later modified to 3.5-5.0 mg/dL.

Because this was the first pediatric study of burosumab, dose adjustments for serum phosphorus <3.5 mg/dL were initially conservative (monthly increases of 0.1 mg/kg Q2W or 0.2 mg/kg Q4W); the maximum dose was set at 1.0 mg/kg Q2W or 2.0 mg/kg Q4W. Based on week-16 PD data, and the prolonged titration needed to reach goal in most patients, the dose increments were increased (to 0.3 mg/kg Q2W or 0.4 mg/kg Q4W), and the maximum dose was changed to 2.0 mg/kg for either group (Q2W or Q4W), with a maximum of 90 mg (protocol amendment 4). There were also provisions for dose reductions (in the same increments) for serum phosphorus above target range (initially 4.5 mg/dL, later 5.0 mg/dL). Rounding of calculated doses to the nearest 10 mg was implemented in protocol 5.

Upon review of additional PD data at 24 weeks and radiographic rickets scores at 40 weeks, the applicant determined that responses were more favorable with Q2W compared to Q4W dosing. Thus, protocol amendment 5 provided for an extension of the study from week 64 to week 160, in which all patients would have Q2W dosing (Q4W patients would have their dose adjusted to the new interval).

Burosumab doses were administered by subcutaneous (SC) injection to the abdomen, upper arms and thighs with rotating sites. All injections were given by study personnel, until protocol amendment 6 (7/7/16) added an option for non-healthcare provider administration under certain conditions.

Oral phosphate and active vitamin D were not allowed in the study, with pre-baseline washout periods of 1 week and 2 weeks respectively, because it was expected that such concomitant treatment may present a safety issue. Nutritional vitamin D was allowed, and supplements were to be provided if serum 25-OH-D levels fell below 20 ng/mL.

Reviewer Comments:

The lack of a control group in this study (either placebo or active control) and other aspects of study design were discussed with the applicant at a meeting on 5/28/14. It was agreed that a placebo arm would be ethically unacceptable, because of the potential for irreversible disability with XLH and the availability of a partially efficacious treatment (phosphate/calcitriol). The Division recommended an active control arm with conventional therapy, to provide context to the data and some information on comparative effectiveness. The applicant cited issues with the use of active-control including the complexity and lack of standardization of conventional therapy, difficulty with blinding, potential difficulty with recruitment of subjects, and differences in short-term goals between treatments (normalization of serum phosphorus would be a potential safety issue with conventional therapy). Also noted was the objectivity of the main endpoints planned (serum phosphorus and other labs, height, radiographic) in comparison to baseline. Because nearly all patients were receiving long-term phosphate/calcitriol prior to enrollment (see below), the protocol was considered to have some features of a “baseline-controlled” study. Ultimately, the applicant decided to defer inclusion of an active control group until the pediatric phase 3 study (which is currently ongoing but with no data yet available) and to conduct a separate, retrospective study of patients receiving phosphate/calcitriol (study CL002), which is discussed in section 8.1.2.

Study Population

Study CL201 enrolled pre-pubescent children (Male/Female, age 5-12 years old, Tanner stage ≤2), with open growth plates. Other key inclusion criteria were:

- XLH diagnosis supported by either genetic testing (*PHEX* mutation) of patient or family member with X-linked inheritance or serum FGF23 level >30 pg/mL
- Fasting serum phosphorus ≤ 2.8 mg/dL
- Serum creatinine within age-adjusted normal range
- Standing height <50th percentile for age and sex
- Radiographic evidence of active bone disease:
 - For the original 30 (“pre-expansion”) patients, rickets in wrists and/or knees and/or femoral/tibial bowing

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- For the ~20 “expansion” patients, a minimum radiographic rickets score (knee RSS ≥ 1.5 , see below)

Reviewer Comments:

The stated rationale for not including patients >12 years old was that open growth plates are needed for optimal evaluation of rickets and growth.

The restriction of the “expansion cohort” to patients with more severe rickets (baseline knee RSS ≥ 1.5) was based on data from the initial 30 patients, which showed that higher-RSS patients had more severe clinical characteristics at baseline and were more likely to show radiographic improvement with treatment (see below).

Key exclusion criteria were:

- Nephrocalcinosis grade 3 (uniformly intense echogenicity throughout medullary pyramids) or 4 (stone formation)
- Serum creatinine above ULN for age
- Hypo- or hypercalcemia
- Evidence of tertiary hyperparathyroidism, as determined by investigator
- Patients receiving therapy with the following prohibited medications, that may affect phosphorus metabolism, were required to discontinue: calcitriol or other vitamin D analogs, oral phosphate, calcimimetics (cinacalcet), systemic corticosteroids, thiazides, ALOH antacids, growth hormone (3 month washout), bisphosphonates
- Planned orthopedic surgery

Study Assessments

There were two screening visits, which included determination of eligibility (x-rays, serum phosphorus and FGF23, *PHEX* genetic testing, height) and discontinuation of any phosphate and/or active vitamin D therapy. Baseline assessments also included XLH related history; physical exam; Tanner staging; vital signs with height and weight; ECG; renal ultrasound and echocardiogram for assessment of ectopic mineralization; 6-minute walk test; POSNA-PODCI questionnaire; and various labs for efficacy and safety.

During the initial Titration Period (weeks 0-16), patients were seen in the clinic every 2 weeks for injections, with serum phosphorus and calcium at every visit and other labs at frequent intervals (including 2-hr urine collections for assessment of Tmp/GFR), and assessment of AEs and concomitant meds.

During the subsequent Treatment Period, clinic visits occurred at 4-week intervals for weeks 16-40 and at approximately 8-week intervals for weeks 40-64. Between these visits, patients were seen at home visits by site staff every 2 weeks for injections, collection of efficacy and safety labs and recording of AEs and vital signs. Knee and hand/wrist x-rays were repeated at week 40

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and 64 visits, and standing long leg x-rays at week 64. Other efficacy assessments of growth, 6MWT and POSNA-PODCI were repeated at weeks 24, 40 and 64. Safety assessments of ECG, echo and renal ultrasound were conducted at weeks 16 and 64.

In the Treatment Extension Period (week 64-160) which is ongoing, clinical visits are planned for approx. 24-week intervals. Home health visits continue every 2 weeks for injections and collection of AEs and concomitant medications.

A Data Monitoring Committee (DMC) met approximately quarterly through week 64 to review study progress including safety data, and to advise the applicant about any needed changes to the protocol.

Study Endpoints

Primary PD endpoint: Serum phosphorus

Serum phosphorus was designated in the protocol as the “primary PD marker of KRN23 efficacy” for this dose-finding study. The phosphorus level was measured at frequent intervals and the 2-week-post-dose levels were used to guide dose adjustments, with a target range of 3.5-4.5 mg/dL (later changed to 3.5-5.0 mg/dL), representing roughly the low-normal to mid-normal range for the 5-12 y/o age group. Because serum phosphorus is subject to diurnal and postprandial variation, samples were collected after a minimum overnight fast of 4 hours, and pre-injection at visits where burosumab was administered. Samples were analyzed at a central lab (b) (4).

Primary clinical efficacy endpoint: Rickets Severity Score (RSS)

Radiographs have long been the gold standard for the diagnosis and evaluation of rickets. Characteristic changes are best seen in the metaphyses of rapidly growing bones: distal radius and ulna, distal femur and proximal tibia. In study CL201, bilateral AP knee and PA hand/wrist radiographs were obtained at screening and at weeks 40 and 64. Healing of radiographic rickets using RSS scores (total, knee and wrist) was included among efficacy endpoints in the protocol. The statistical plan designated RSS total score (change from baseline) as the primary clinical efficacy endpoint., and RSS knee and wrist subscores as secondary endpoints.

The RSS was developed for nutritional rickets (deficiency of vitamin D and/or calcium). In the absence of other available radiographic scoring methods for rickets, including XLH, the applicant adapted the RSS to study CL201. Using the more severely affected wrist and knee (left or right), the RSS assigns scores for typical rachitic features: for distal radius and ulna, widening of the cartilaginous growth plate, irregular lucency of the metaphyseal margin and concave cupping of metaphysis; and for distal femur and proximal tibia, lucency and widening of the zone of provisional calcification (score is multiplied by 0.5 if only one condyle or plateau is involved). RSS total scores can range from 0 (no rickets) to 10 (sum of worst possible scores of 2, 2, 3, 3 for radius, ulna, femur and tibia respectively). Knee and wrist subscores (maximum

scores = 6 and 4 respectively) have also been used in some clinical studies. Films are read individually for the RSS, without comparison to other films from the patient. Open growth plates are required for assessment of the RSS. (Thacher 2000)

In nutritional rickets, inter- and intra-observer correlation of RSS scores is high; total, wrist and knee RSS correlate with each other and with serum alkaline phosphatase levels, another measure of rickets activity; and the RSS was found useful in assessing the response to therapy of nutritional rickets, which occurs within ~6 months. (Thacher 2000 and Thacher 2016)

Prior to this development program, there were no available data on use of the RSS in XLH, a condition with radiographic features that are generally similar to nutritional rickets, but with some possible differences. Literature reports indicate that XLH related rickets may be more likely than other types to involve lower (vs. upper) extremities, and to feature prominent leg bowing, likely related to greater chronicity of the disease, and genu varum in which the distal femoral/ proximal tibial growth plates are often more affected medially than laterally, perhaps due to compressive stress (Shore 2013). Therefore, RSS scores of children with XLH generally fall in the range of 0 to 4.0, which is somewhat lower than the typical range for children with nutritional rickets, while other features that occur more commonly in XLH compared to nutritional rickets (e.g. bowing, tibial torsion) are not measured by the RSS.

In study CL201, knee and wrist images are centrally read and RSS calculated by [REDACTED] (b) (4), who is blinded to patient data and to radiograph sequence. As an additional blinding measure, images from CL201 patients were intermixed randomly with those of untreated XLH patients; for the week 40 analysis, the untreated-comparator images were from CL201 patients taken prior to burosumab treatment; and for the week 64 analysis, the comparator images were from patients in the historical control study, CL002 (see section 8.1.2).

Reviewer Comment:

The RSS has been used in one other drug development program: asfotase alfa (Strensiq, BLA 125513, approved 2016), an enzyme replacement therapy for hypophosphatasia (HPP). Childhood rickets is among the prominent clinical features of HPP, though the mechanism differs from nutritional rickets or XLH. Among 8 juvenile-onset HPP patients (age 6-12 y/o), median RSS scores declined from 3.0 at baseline, to 1.0 and 0.5 at months 36 and 60 of treatment, respectively, and showed minimal change in an untreated natural history cohort. In that application, the RSS was not specifically validated for the HPP population, however correlations of RSS with height, functional scores and bone biopsy parameters of osteomalacia were seen.

Similarly, in this application, the RSS has not been specifically validated for XLH, and DBRUP initially had concerns about whether the baseline scores (see results below) may be too low on a 0-10 scale to adequately discriminate clinically meaningful improvement. To support use of the RSS, the applicant provided data indicating trends of more severe clinical features in children with XLH and higher RSS (see below).

Secondary Clinical Efficacy Endpoints

Radiographic Global Impression of Change (RGI-C)

To supplement the RSS, the applicant developed the RGI-C, another scale for scoring rickets based on the same wrist and knee X-rays. The RGI-C evaluates some of the growth plate and metaphyseal changes used in the RSS, as well as certain other features (RGI-C can still be assessed after growth plates have closed), so there is some overlap between these scales; the applicant considers RSS and RGI-C to be complementary. Unlike the RSS, the RGI-C compares films from two different timepoints to assess improvement or worsening of rickets. The RGI-C reader is asked to integrate the findings qualitatively into a score for the changes from baseline:

- -3 = severe worsening
- -2 = moderate worsening
- -1 = minimal worsening
- 0 = no change
- +1 = minimal healing
- +2 = substantial healing
- +3 = complete or near complete healing

In study CL201, each of 3 pediatric radiologists contracted by the central imaging facility (b) (4) independently examine paired images from a given patient, including knee and wrist xrays at screening, weeks 40 and 64, and standing long leg xrays at screening and week 64. The reader compares the screening image (on their left) with the corresponding image at week 40, 64 or later timepoint (on their right), and assigns RGI-C scores for the wrist, the knee, and a global score (which represents an overall impression of changes at wrist and knee, rather than a calculation based on the wrist and knee scores). The scores from the 3 readers are averaged to generate overall RGI-C scores used for the secondary efficacy endpoint analyses. As with the RSS, readers were blinded to clinical data.

In addition to these scores for overall change used for secondary efficacy endpoints, RGI-C evaluators recorded the presence or absence of specific metaphyseal abnormalities (lucency, separation, fraying and concavity) at 5 skeletal sites (distal radius/ulna; distal femur; proximal tibia/fibula).

Reviewer Comment:

The applicant believes that the side-by-side comparison of pre- and post-treatment images in the RGI-C is an advantage as it resembles the approach used in clinical practice. However unlike the RSS, awareness of image sequence may bias the interpretations if the reader is not blinded to treatment.

Lower extremity deformity: RGI-C long leg scores

Standing long leg radiographs were obtained at screening and at week 64. Using RGI-C scales of

worsening or healing as defined above for changes in rickets (-3 to +3), the same 3 radiologists graded changes from baseline to week 64 in deformities including bowing, knock knees and tibial torsion.

Growth

Impaired growth, particularly of the legs, is one of the predominant clinical features of XLH. Standing height (stadiometer), sitting height, arm length and leg length were measured by a physical therapist at baseline and weeks 16, 28, 40, 56 and 64. Height measures were converted to age- and gender-adjusted Z-scores and percentiles, to allow comparison to reference data. In addition, growth velocity was evaluated by comparison to the patient's historical growth from records where available.

Reviewer Comment:

In the absence of a control group, changes in height or in height velocity are inherently difficult to interpret. Change in height Z-score provides context because of the comparison to reference data and is the predominant growth parameter used in labeling of human growth hormone products. The FDA Guidance for Industry: Orally inhaled and intranasal corticosteroids: evaluation of the effects on growth in children (2007) recommends growth velocity as a primary endpoint, but within the context of a placebo controlled study, and recommends height Z-score as a secondary endpoint. For measurements of sitting height, arm length and leg length, it does not appear that adequate pediatric reference data for age/sex (Z-scores) are available.

Secondary Pharmacodynamic Endpoints

in addition to serum phosphorus, there were two "key" PD endpoints: serum 1,25-(OH)₂-vitamin D and TmP/GFR, which are central to the pathophysiology of XLH (representing, respectively, 1- α -hydroxylase activity and renal phosphate reabsorptive capacity), and purported mechanism of action of burosumab.

Serum alkaline phosphatase

Both total alkaline phosphatase (ALP) and bone-specific ALP (BALP) are usually elevated in children with XLH and other forms of rickets. Treatment of XLH with phosphate/calcitriol generally normalizes ALP levels within ~6-12 months.

Reviewer Comment:

ALP or BALP are used by many clinicians as a marker of rickets disease activity and to monitor therapeutic response (e.g. to vitamin D in nutritional rickets or conventional therapy for XLH), in part to avoid frequent x-rays. It is not clear how much additional information these measures provide when serial radiographs are available.

Other secondary PD endpoints included urine phosphorus, tubular reabsorption of phosphate (TRP), fractional excretion of phosphorus (FEP) and serum markers of bone turnover (P1NP, CTx).

Walking ability: A 6-minute walk test (6MWT) was administered at intervals, and total distance walked (in meters) was compared to predicted normal values based on age, sex and height.

Functional disability and pain: A standardized parent questionnaire used to assess pediatric musculoskeletal disorders, the Pediatric Orthopedic Society of North America – Pediatric Outcomes Data Collection Instrument (POSNA-PODCI), was administered. The PODCI has 5 domains (Upper Extremity Function, Transfers and Mobility, Physical Function and Sports, Pain-free Comfort and Happiness and Satisfaction). PODCI scores are usually normalized to a healthy population with mean score of 50 and SD of 10.

Reviewer Comment

As the applicant was informed at IND meetings, the 6MWT may be an appropriate endpoint for pediatric XLH given the extent of gait difficulties in these patients, but has a large voluntary component and FDA is cautious about use of 6MWT in unblinded studies for labeling; in addition, 6MWT is not acceptable for use in children <6 years old. The applicant also was informed that for various reasons the POSNA-PODCI is not acceptable for the proposed context of use for regulatory purposes, in addition to the issue of lack of controls and blinding. While some of the 6MWT and POSNA-PODCI data at study baseline are of interest clinically, the post baseline data do not contribute to the efficacy evaluation because of these issues, and the applicant does not seek labeling claims based on these endpoints, therefore they are not discussed in this review.

In summary, DBRUP considers the efficacy endpoints of serum phosphorus, rickets and bowing by xray, and growth to be clinically relevant and objective outcomes for this pediatric investigation. Serum ALP and BALP also appear to be appropriate endpoints, potentially relevant for labeling because they are used by clinicians treating rickets. Osteomalacia (by bone histomorphometry) would also be a highly relevant efficacy endpoint, but such data were not considered essential in children, given the invasiveness of bone biopsy and the applicant's plan to obtain biopsy data in adults with XLH (study CL304, see section 8.1.5).

Safety endpoints included AEs and SAEs; injection site reactions; assessment of potential ectopic mineralization (serum Ca and phosphorus, urinary Ca and creatinine, renal ultrasound, echocardiogram); immunogenicity; routine safety labs; pregnancy tests; concomitant meds; vital signs and physical exams.

Statistical Analysis Plan

Sample size

The applicant proposed a sample size of 50 subjects (25 subjects each regimen of Q2W and Q4W) to detect a mean change from baseline of 0.5 in RSS total with a standard deviation of 0.5 at the two-sided 0.05 level of significance with at least 90% power. A sample size of at least 10 subjects per cohort would provide at least 90% power to detect a serum phosphorus increase from baseline of at least 0.8 mg/dL, assuming a standard deviation of 0.7 mg/dL or smaller.

Interim analysis

Analyses were pre-specified at four timepoints during the titration and treatment periods (Week 16, Week 24, Week 40 and Week 64) with the primary analysis occurring at Week 40. Descriptive analyses with no formal hypothesis testing were pre-specified at both Week 16 and Week 24. Additional interim analyses were planned at Week 88 during the extension period, and at Week 160 at the end of extension period.

Analysis Populations

The following analysis populations were defined in the statistical analysis plan:

- Intent to treat set (ITT): All subjects who received at least one dose of study therapy and had at least one post-dose measurement.
- Safety analysis set: All subjects who received at least one dose of study therapy.
- Pharmacokinetic and Pharmacodynamic (PK/PD) analysis set: All subjects who received at least one dose of therapy and had evaluable serum data.

Handling of Missing and Incomplete Data

In general, missing data were treated as missing, unless otherwise specified in the statistical analysis plan. When a change from baseline was assessed, only patients with a baseline and at least one post-baseline measurement were included in the analysis.

Efficacy Analysis Methods

All efficacy analyses were done using the ITT set (Q2W, Q4W and overall). The observed value and the change from baseline for each efficacy endpoint was summarized using descriptive summary statistics. In addition, the following efficacy endpoints were analyzed using the pre-specified approaches in the statistical analysis plan.

Rickets Severity Scale (RSS) Total Score

The change from baseline of RSS total score, the primary clinical efficacy endpoint, was analyzed using a generalized estimating equations (GEE) model that included the baseline RSS total score, regimen group, study visit and interaction between regimen and study visit as categorical variables (factors), and baseline RSS total score as the covariate, with an exchangeable covariance structure. Model based estimates of the changes from baseline, standard errors and corresponding 95% confidence intervals (CIs) were provided along with p-values for assessing statistical significance. The data up to Week 64 was included in the model. The difference between the two regimens (Q2W and Q4W) was summarized with a 95% CI and no formal hypothesis testing of the difference between regimens was done.

The RSS total score was also evaluated by subgroups defined by age, sex, race, region and baseline RSS respectively.

A responder analysis of the RSS total score, a clinically important piece of information, was

evaluated as follows:

- Percentage of subjects with a RSS total score reduction from baseline of at least 1.0 among subjects with a baseline RSS total score of at least 1.0
- Percentage of subjects who healed completely among subjects with a baseline total score > 0

RSS Knee and Wrist Scores

The change from baseline in RSS knee and wrist scores were analyzed using the same approach as for the change from baseline in RSS total score.

Radiographic Global Impression of Change (RGI-C) Score

The RGI-C score was analyzed using the same GEE model as for the RSS total score above.

Growth

Change from baseline in the standing height Z score was analyzed using a GEE model with standing height Z score at selected study visits as the independent variable, baseline height, age and sex as covariates, and regimen group, study visit and interaction between regimen and study visit as categorical independent variables with exchangeable covariance structure. Percentile of standing height and the change from baseline were summarized by descriptive statistics.

The growth velocity of standing height in cm/year was estimated for the pre-treatment (e.g. within 2 years prior to Baseline) and post-treatment periods for each subject. The average slope of growth velocity in cm/year was descriptively summarized for each treatment period. A one sample T-test was used to assess the difference of growth velocities in cm/year between pre-treatment period and post-treatment period.

Walking Ability (6MWT) and Functional Disability and Pain (POSNA-PODCI)

Reviewer Comment:

Please refer to the endpoint section. The 6MWT and POSNA-PODCI endpoints are not interpretable in this open label, uncontrolled study.

Pharmacodynamic Endpoints

Descriptive statistics for the PD endpoints and their change from baseline and percent change from baseline were presented by regimen and overall. Graphs showing the change over time in key PD parameters for both the observed measure and its change from baseline were provided by regimen. Subgroup analysis was also performed by baseline RSS total score ≥ 1.5 or < 1.5 .

Multiplicity Control

No multiplicity control of type I error was done in the study.

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Protocol Amendments

The original protocol of study CL201 was dated 2/24/14.

Protocol amendment 1 (dated 5/7/14) expanded the height criterion for study inclusion from <25th percentile to <50th percentile.

Protocol amendment 2 (7/2/14) implemented minor changes.

Protocol amendment 3 (3/2/15) expanded the study from ~30 to ~50 patients with the added inclusion requirement of knee RSS ≥ 1.5 .

Protocol amendment 4 (4/22/15) raised the upper limit of the target serum phosphorus from 4.5 to 5.0 mg/dL, accelerated dose titration increments, and increased the maximal Q2W dose to 2.0 mg/kg.

Protocol amendment 5 (8/28/15) added the Treatment Extension Period and stipulated that Q4W patients would transition to Q2W after week 64.

Protocol amendment 6 (7/7/16) added an option for non-HCP administration of study drug under certain conditions.

Study Results

Compliance with Good Clinical Practices

The applicant attests that study CL201 has been conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

Study CL201 is among the covered clinical studies, as defined by 21 CFR 54.2(e), which provide the primary evidence establishing the effectiveness and safety of burosumab (see Appendix 15.2). The applicant has adequately disclosed financial interests/arrangements with the clinical investigators as recommended in FDA guidance and no concerns are raised about the integrity of the data.

Patient Disposition

A total of 52 pediatric subjects were enrolled into the study. The 4 US sites enrolled most of the patients (36/52 = 69%). Among 27 patients who failed screening, the most common reason was lack of radiographic evidence of bone disease (18 patients).

Table 47 Study CL201: Enrollment by site/country

Site #	Investigator	Site Location	Country	# patients screened	# patients enrolled
138	Carpenter	Yale Univ.	USA	22	16
139	Portale	UCSF	USA	9	8
140	Whyte	Shriners Hosp. St. Louis	USA	11	6
141	Linglart	Hôpital Bicetre, Paris	France	6	2
148	Hogler	Birmingham Childrens	UK	5	2
149	Padidela	Manchester	UK	6	5
150	Boot	Groningen	Netherlands	6	4
152	Van't Hoff	Great Ormond Hosp. London	UK	3	3
156	Imel	Indiana Univ.	USA	11	6
Total USA				53	36
Total UK				14	10
Total France				6	2
Total Netherlands				6	4
Total all sites				79	52
Source: Listing 16.1.4					

Patients were randomized 1:1 to the Q2W and Q4W groups (N=26 each). The first 36 patients enrolled comprised the “pre-expansion” group and the last 16 were the “expansion group”, for which an added requirement of baseline knee RSS ≥ 1.5 applied. All 52 patients completed at least 64 weeks on study, with no discontinuations, and were included in all efficacy and safety assessments. Thus, the ITT, safety analysis set and PK/PD analysis set have equivalent subject numbers. As of the cut-off date for the 120-day safety update (5/8/17), all 52 patients were continuing burosumab treatment in the study extension.

Protocol Violations/Deviations

There were 3 patients with enrollment criteria deviations that were waived: 2 patients who had screening serum phosphorus levels of 2.9 mg/dL (inclusion criteria specified ≤ 2.8 mg/dL); and 1 patient who had plate removal surgery planned (and performed during the study). Three patients had single instances at which the dose of burosumab administered differed from the calculated dose by 6, 8 or 20 mg. The remaining protocol deviations were generally minor and would have no significant effect on the study results.

Demographic and other baseline characteristics

Among the 52 enrolled children, there were 28 girls and 24 boys, with a mean age of 8.5 years; most were white and non-Hispanic (Table 48 below). Tanner stage was 1 for 38 patients, and 2 for the other 14. All except 2 of the children had been previously treated for XLH with conventional therapy, beginning at an average age of ~ 2 years and for an average duration of

almost 7 years. At baseline (following conventional therapy washout), patients had low serum phosphorus (mean 2.33 mg/dL, reference range for age approx. 3.2-6.1 mg/dL); low TmP/GFR (mean 2.08 mg/dL, LLN is ~2.6 mg/dL); serum 1,25(OH)₂D generally WNL; growth delay (mean height Z-score -1.9, percentile 8.7); and significant bone disease. Pertinent past histories included bowing of the limbs (96% of patients), difficulty with gait (77%), short stature (69%), bone or joint pain (69%), intoeing (58%) and dental abscesses (54%). *PHEX* mutation analysis, which cannot identify all clinically significant variants, was positive for pathogenic mutations in 45 patients; the other 7 patients had been clinically diagnosed with XLH and met the added inclusion requirement of serum FGF23 > 30 pg/mL. Baseline renal ultrasound showed nephrocalcinosis (score of 1 or 2) in 35% of patients.

Baseline xrays showed rickets (RSS > 0) in the majority of patients at the wrists (65%), knees (92%) and overall (94%), with mean total RSS of 1.80. Specific metaphyseal abnormalities assessed for the RGI-C (lucency, separation, fraying and/or concavity) were identified at baseline in the distal radius (64% of patients), distal ulna (92%), distal femur (100%), proximal tibia (92%) and proximal fibula (42%). Standing long leg x-rays showed varus abnormalities in femur, tibia and/or fibula in 73% of patients and valgus abnormalities in 10%.

Table 48 Study CL201: Demographics and Baseline Characteristics, by treatment regimen (ITT)

	Q2W (N=26)	Q4W (N=26)	Total (N=52)
Sex – n (%)			
Male	12 (46)	12 (46)	24 (46)
Female	14 (54)	14 (54)	28 (54)
Age			
Mean years (SD)	8.7 (1.7)	8.3 (2.0)	8.5 (1.9)
Min, max (years)	5, 12	5, 12	5, 12
Race – n (%)			
White	23 (89)	23 (89)	46 (89)
Black or African American	2 (8)	0	2 (4)
Other	1 (4)	3 (12)	4 (8)
Ethnicity – n (%)			
Hispanic or Latino	0	2 (8)	2 (4)
Not Hispanic or Latino	26 (100)	24 (92)	50 (96)
Ever treated with conventional therapy – n (%)			
Yes	24 (92)	26 (100)	50 (96)
No	2 (8)	0	2 (4)
Age when conventional therapy initiated (years)			
Mean	2.2	1.9	2.1
Min, max	0.0, 5.7	0.0, 5.0	0.0, 5.7
Mean duration of conventional therapy (years)	7.0	6.7	6.9
Rickets Severity Score (RSS) at baseline (mean)			
Wrist RSS	0.71	0.48	0.60
Knee	1.21	1.19	1.20
Total RSS	1.92	1.67	1.80
Height Z-score			
Mean	-1.72	-2.05	-1.89
Min, max	-4.0, -0.1	-4.1, -0.6	-4.1, -0.1
Height percentile, mean	11.1	6.2	8.7
BMI, mean	20.7	19.9	20.3
Serum phosphorus (mg/dL)			
Mean	2.38	2.28	2.33
Min, max	2.0, 3.5	1.8, 3.0	1.8, 3.5
TmP/GFR (mg/dL), mean	2.18	1.98	2.08
Serum 1, 25-vitamin D (pg/mL), mean	41.3	41.4	41.3
PHEX Mutation – n			
Positive	23	22	45
Negative	1	1	2
Likely pathogenic	1	0	1
Variant of unknown significance	1	3	4

Source: CSR Table 14.1.2.1.1.1.

Patients with greater or lesser severity of rickets at baseline (RSS ≥ 1.5 and RSS < 1.5 respectively, based on the median value for the initial 36 patients) are compared in the table below. Higher-RSS patients were more likely to be female and were slightly older. The higher- and lower-RSS groups were similar in regard to previous treatment with conventional therapy (age at initiation and duration of exposure). Specific metaphyseal abnormalities (lucency, separation, fraying and concavity) were consistently more prevalent at various sites in higher RSS patients, though all lower RSS patients exhibited growth plate abnormalities and bowing deformities. The patients with higher RSS tended to be more severely affected in other features including more severe growth delay, higher serum alkaline phosphatase, lower serum phosphorus and TmP/GFR, reduced walking ability (6MWT), and lower scores for functional disability and pain as measured by the POSNA-PODCI.

Table 49 Study CL201: Demographics and Baseline Characteristics, by baseline rickets severity (ITT)

	Higher-RSS (≥1.5) (N=34)	Lower-RSS (<1.5) (N=18)	Total (N=52)
Sex – n (%)			
Male	14 (41)	10 (56)	24 (46)
Female	20 (59)	8 (44)	28 (54)
Age			
Mean years (SD)	8.7 (1.8)	8.1 (2.1)	8.5 (1.9)
Min, max (years)	5, 12	5, 12	5, 12
Height Z-score			
Mean	-2.12	-1.44	-1.89
Min, max	-4.1, -0.5	-3.4, -0.1	-4.1, -0.1
Height percentile, mean	5.8	14.0	8.7
Rickets Severity Score (RSS) at baseline (mean)			
Wrist RSS	0.85	0.11	0.60
Knee	1.60	0.44	1.20
Total RSS	2.46	0.56	1.80
Serum alkaline phosphatase (U/L)			
Mean	497	388	459
Min, max	325, 706	237, 532	237, 706
Serum phosphorus (mg/dL)			
Mean	2.21	2.55	2.33
Min, max	1.8, 2.7	2.0, 3.5	1.8, 3.5
TmP/GFR (mg/dL), mean	2.00	2.21	2.08
6-Minute Walk Test			
Mean distance (m)	468	511	483
Mean percent of predicted distance*	77.4	86.0	80.4
POSNA-PODCI normative scores** , mean			
Sports/Physical functioning scale	29.6	40.9	33.4
Pain/comfort scale	29.9	45.3	35.0
Global functioning scale	32.3	45.2	36.6
*based on age, gender and height **normative healthy population mean = 50, 10 points = 1 SD, LLN = 40 Source: CSR Table 14.1.2.1.1.1, Table 14.1.2.1.2.1, Table 14.1.2.1.3.1, Table 14.2.1.5.1.1, Table 14.2.1.5.2.1, Table 14.2.1.5.3.1, Table 14.2.1.5.10.1, Table 14.2.1.5.11.1, Table 14.2.1.5.12.1, Table 14.2.1.4.1.1, Table 14.2.1.4.2.1, Table 14.2.1.4.3.1			

Reviewer Comment:

These data, demonstrating generally more severe disease in higher-RSS patients, help support use of the RSS as a clinically relevant endpoint, as the RSS has not previously been systematically used or validated in XLH.

Treatment Exposure, Compliance, Concomitant Medications

Compliance was excellent in study CL201. Between baseline and week 64, there were only 3 patients (two in Q2W group and one in Q4W group) who missed a scheduled visit/dose (1 dose each). There were no reports of patients receiving prohibited medications (phosphate, calcitriol, growth hormone), or glucocorticoids for >1 week.

Starting doses and dose titrations were conservative in this first pediatric study of burosumab. Therefore, at week 40, dose adjustments had been completed in only 44 of the 52 patients, and the remaining 8 patients underwent further dose adjustments up to week 60. For the Q2W group at weeks 40-64, the average steady-state dose was approximately 1.0 mg/kg, with a range of 0.4-2.0 mg/kg. For the Q4W group, as expected, average dose was somewhat higher. At week 64, Q4W patients transitioned to Q2W dosing, initially at ~60% of their previous Q4W dose followed by titration, and dose adjustments continue to be allowed for any patient with serum phosphorus outside normal range throughout this long-term extension. After the regimen change at week 64, mean Q2W dose (in all patients) declined to ~0.90-0.92 mg/kg and remained stable to week 102.

Table 50 Study CL201: Burosumab dose (mg/kg) at selected timepoints

	Q2W N=26		Q4W N=26	
	Mean dose	Dose range	Mean dose	Dose range
Baseline	0.24	0.1-0.3	0.48	0.2-0.6
Week 16	0.73	0.3-1.5	1.15	0.2-2.0
Week 40	0.98	0.4-2.0	1.50	0.6-2.0
Week 64	1.05	0.4-2.0	1.57	0.6-2.0
Week 88* (n=18)	0.91	0.4-1.8	-	-
Week 102* (n=18)	0.92	0.4-1.8	-	-

*patients randomized to Q2W in pre-expansion group
 Source: CSR ADEX

Patients with higher baseline RSS scores ≥ 1.5 required higher doses to achieve the serum phosphorus target range. For example in the Q2W group, mean doses in the higher versus lower RSS subgroup were 1.15 versus 0.64 mg/kg at week 40, and 1.25 versus 0.67 mg/kg at week 64. Presumably, this was related to the differing baseline serum phosphorus levels in these subgroups (2.21 vs. 2.55 mg/dL) and different disease severity.

Reviewer Comment:

For pediatric labeling, the applicant proposes a starting dose of 0.8 mg/kg Q2W (rounded to the nearest 10 mg), with dose increase in two steps to a maximum of ~2.0 mg/kg Q2W (max. 90 mg) as needed to achieve normal serum phosphorus. Guidelines for reducing dose based on hyperphosphatemia are also proposed for labeling. In this study, dose was reduced at

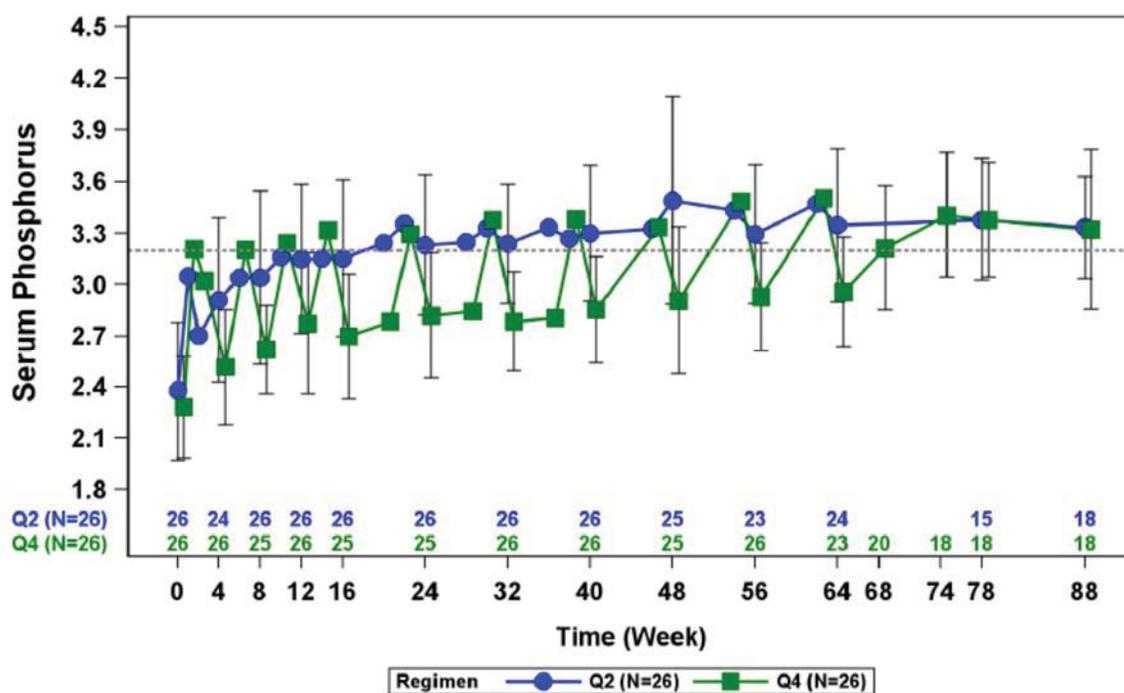
phosphorus levels (4.5-5.0 mg/dL) that were well below the ULN.

Efficacy Results

Primary PD endpoint – Serum Phosphorus

Serum phosphorus, which is discussed in depth in section 6 of this review, is briefly summarized here. Upon reaching steady state dosing (~week 40-64), mean serum phosphorus in the Q2W group had increased from a baseline mean of 2.4 mg/dL to ~3.3 mg/dL (normal range for age ~3.2-6.1 mg/dL). In the Q4W group, there was a peak-and-trough pattern in serum phosphorus as the effect waned toward the end of the dosing cycles, although pre-dose (trough) levels remained above baseline (figure below). Changes from baseline were generally similar between higher-RSS and lower-RSS patients.

Figure 35 Study CL201: Serum phosphorus, mean (SD) level (mg/dL) by regimen/visit (PK/PD Analysis Set)



Dotted line represents approximate LLN for age group.
 Source: Fig. 14.2.3.1.1.99, submitted 1/17/18

Among the 52 patients, 49 (94%) had at least one serum phosphorus level within the designated normal range (3.2-6.1 mg/dL) by week 64. Of the 3 remaining patients, two (b) (6) had substantial increases in serum phosphorus from baseline at most timepoints, as well as decrease in RSS scores, and one patient, (b) (6), a 5 years old male in Q4W group, had baseline serum phosphorus of 2.5 mg/dL and post-baseline values of 2.1-3.1

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mg/dL, and baseline RSS total score of 0.5 which was unchanged at week 64. No patient had any episode of hyperphosphatemia (see discussion in section 8.3.5).

Based on these results, the Q4W patients were transitioned to Q2W dosing beginning at week 64. The main rationale was that children have high phosphate requirements (and higher serum levels) compared to adults because of demand by growing bones, and optimal improvement in rickets may require serum phosphorus to be maintained in normal or near-normal range continuously. This hypothesis appeared to be supported by interim rickets data showing trends of more favorable results with Q2W versus Q4W dosing (see below).

Primary clinical efficacy endpoint – Rickets Severity Scale (RSS) Total Score

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At baseline, the mean RSS total score for the overall study population (N=52) was 1.80. At Week 40, the overall mean change from baseline in RSS total score declined by 0.89 (a 50% decline from baseline). At Week 40, there was a numerically greater decline in the mean change from baseline in RSS total score in the Q2W group (-1.06) compared to the Q4W group (-0.73) (Table 51). These improvements were maintained and essentially unchanged at Week 64 (a 51% decline from baseline for the overall study population).

Table 51 Study CL201: RSS total score, change from baseline by dose regimen (ITT)

Visit	Statistics	Q2W (N=26)	Q4W (N=26)	Overall (N=52)
Baseline	Mean (SD)	1.92 (1.17)	1.67 (1.00)	1.80 (1.09)
Week 40 ^a	Mean (SD)	0.75 (0.55)	1.06 (0.54)	0.90 (0.56)
	Change from Baseline ^b			
	LS mean (SE)	-1.06 (0.11)	-0.73 (0.10)	-0.89 (0.07)
	95% CI	(-1.28, -0.85)	(-0.92, -0.53)	(-1.04, -0.75)
	P-value	<0.0001	<0.0001	<0.0001
	Difference (Q2W-Q4W) (95% CI)	-0.33 (-0.63, -0.04)		
Week 64	Mean (SD)	0.81 (0.60)	0.94 (0.52)	0.88 (0.56)
	Change from Baseline ^b			
	LS mean (SE)	-1.00 (0.11)	-0.84 (0.10)	-0.92 (0.07)
	95% CI	(-1.22, -0.79)	(-1.03, -0.65)	(-1.07, -0.78)
	P-value	<0.0001	<0.0001	<0.0001
	Difference (Q2W-Q4W) (95% CI)	-0.16 (-0.45, 0.13)		

CI = confidence interval; GEE = generalized estimation equation; ITT = intent to treat; LS = least squares; Q2W = every 2 weeks; Q4W = monthly; RSS = Rickets Severity Score
^a Primary efficacy endpoint
^b LS mean, p value, and CI per GEE model, which included visit, regimen, visit by regimen as factors, and RSS total score at baseline as a covariate, with exchangeable covariance structure.
 Source: CSR Table 14.2.1.1.1.1

Overall, at baseline, there were 3 patients with a total RSS score = 0 and 49 patients with a total RSS score > 0. Overall, the percentage of patients who healed completely (i.e., had an RSS total score = 0 at Week 64) among patients with a baseline RSS total score > 0 was 14% (7/49), including 24% (6/25) of patients receiving Q2W dosing and 4% (1/24) of patients receiving Q4W dosing.

Primary endpoint subgroups

The following six RSS total score subgroup analysis results presented below are descriptive in nature and are intended to further describe the efficacy results in clinically important subgroups. The results for each subgroup are presented for each dosing regimen and for the combination of both dosing regimens. The six subgroups are age, gender, race/ethnicity,

baseline RSS total score subgroup, region, and study site.

RSS total score by age

At Week 40 and Week 64 for each dosing regimen and for the combination of both dosing regimens, mean RSS total scores decreased from baseline within each age subgroup and the mean changes from baseline in RSS total score were similar between the two age subgroups (5 to < 9 years vs 9 to 12 years).

Table 52 Study CL201: RSS total score, change from baseline by Age group and regimen (ITT)

Visit	Subgroup	Q2W N=26		Q4W N=26		Overall N=52	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	5 to <9 Years	10	1.40 (1.02)	13	1.96 (0.99)	23	1.72 (1.02)
	9 to 12 Years	16	2.25 (1.17)	13	1.38 (0.96)	29	1.86 (1.15)
Week 40	5 to <9 Years	n	LS mean change (SE) (95% CI)	n	LS mean change (SE) (95% CI)	n	LS mean change (SE) (95% CI)
		10	-0.93 (0.16) (-1.24, -0.62)	13	-0.74 (0.14) (-1.02, -0.47)	23	-0.84 (0.11) (-1.05, -0.63)
	9 to 12 Years	16	-1.09 (0.15) (-1.38, -0.80)	13	-0.77 (0.15) (-1.07, -0.48)	29	-0.93 (0.10) (-1.12, -0.74)
		10	-0.78 (0.15) (-1.08, -0.49)	13	-0.82 (0.12) (-1.06, -0.59)	23	-0.80 (0.10) (-0.99, -0.61)
Week 64	9 to 12 Years	16	-1.09 (0.15) (-1.38, -0.80)	13	-0.93 (0.16) (-1.24, -0.61)	29	-1.01 (0.10) (-1.21, -0.81)

LS mean and 95% CI for change from baseline per GEE model, which included visit, regimen, visit by regimen as factors, and RSS total score at baseline as a covariate, with exchangeable covariance structure
 Source: CSR Table 14.2.1.1.99.8.1 Table 14.2.1.1.99.8.2

RSS total score by gender

Overall, mean baseline RSS total scores were slightly higher for female than male subjects (1.96 versus 1.60, respectively), and mean decreases to Week 64 were greater for female than male subjects (-1.27 versus -0.52, respectively). Similar findings are seen when comparing by sex for each dosing regimen.

Table 53 Study CL201: RSS total score, change from baseline by gender group and regimen (ITT)

Visit	Subgroup	Q2W (N=26)		Q4W (N=26)		Overall (N=52)	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	Boys	12	1.67 (0.89)	12	1.54 (1.01)	24	1.60 (0.93)
	Girls	14	2.14 (1.37)	14	1.79 (1.01)	28	1.96 (1.19)
		n	LS mean change (SE) (95% CI)	n	LS mean change (SE) (95% CI)	N	LS mean change (SE) (95% CI)

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Week 40	Boys	12	-0.70 (0.17) (-1.03, -0.37)	12	-0.46 (0.15) (-0.75, -0.18)	24	-0.58 (0.11) (-0.80, -0.37)
	Girls	14	-1.37 (0.13) (-1.63, -1.11)	14	-0.95 (0.13) (-1.20, -0.69)	28	-1.16 (0.09) (-1.34, -0.98)
Week 64	Boys	12	-0.45 (0.10) (-0.65, -0.25)	12	-0.59 (0.14) (-0.86, -0.32)	24	-0.52 (0.08) (-0.69, -0.36)
	Girls	14	-1.48 (0.12) (-1.72, -1.24)	14	-1.05 (0.14) (-1.32, -0.79)	28	-1.27 (0.09) (-1.45, -1.09)
LS mean and 95% CI for change from baseline per GEE model, which included visit, regimen, visit by regimen as factors, and RSS total score at baseline as a covariate, with exchangeable covariance structure Source: CSR Table 14.2.1.1.99.8.3 Table 14.2.1.1.99.8.4							

RSS total score by race/ethnicity

The subgroup analysis of RSS by race/ethnicity was not conducted because 89% (46/52) of patients were White and 96% (50/52) of patients were not Hispanic or Latino.

RSS total score by Baseline RSS total score subgroup

In pediatric patients with a higher baseline RSS total score (≥ 1.5 ; n=34), the RSS total score decreased by 1.49 at Week 40 and by 1.44 at Week 64 from a baseline score of 2.46. Decreases are also seen for each dosing regimen.

Overall, in patients with a lower baseline RSS total score (< 1.5 ; n=18), the RSS total score did not decrease from baseline at Week 40 and Week 64. Similar findings are seen for each dosing regimen.

Table 54 Study CL201: RSS total score, change from baseline by RSS total score subgroup and regimen (ITT)

Visit	Subgroup	Q2W N=26		Q4W N=26		Overall N=52	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	Higher RSS	17	2.62 (0.78)	17	2.29 (0.56)	34	2.46 (0.69)
	Lower RSS	9	0.61 (0.33)	9	0.50 (0.35)	18	0.56 (0.34)
Week 40	Higher RSS	17	LS mean change (SE) (95% CI) -1.68 (0.11) (-1.89, -1.47)	17	LS mean change (SE) (95% CI) -1.29 (0.15) (-1.58, -1.00)	34	LS mean change (SE) (95% CI) -1.49 (0.56) (-1.66, -1.31)
	Lower RSS	9	0.14 (0.22) (-0.28, 0.57)	9	0.30 (0.09) (0.13, 0.47)	18	0.22 (0.12) (-0.01, 0.45)
Week 64	Higher RSS	17	-1.44 (0.13) (-1.70, -1.19)	17	-1.44 (0.14) (-1.70, -1.17)	34	-1.44 (0.09) -1.62, -1.26
	Lower RSS	9	-0.13 (0.14) (-0.40, 0.14)	9	0.25 (0.12) (0.00, 0.49)	18	0.06 (0.09) (-0.12, 0.24)

LS mean, 95% CI and p value for change from baseline per GEE model, which included visit, regimen, visit by regimen as factors, and RSS total score at baseline as a covariate, with exchangeable covariance structure
 Source: CSR Table 14.2.1.1.2.1, Table 14.2.1.1.3.1

Reviewer Comment:

As the applicant states, patients with low RSS at baseline have little or no room for improvement in scores, so these data are not unexpected. Patients with low RSS represented approximately 1/3 of the study population.

RSS total score by region and study site

Overall, among the 36 U.S. patients (69% of total study population), mean RSS total score at baseline was similar to non-U.S. patients. Overall, at Weeks 40 and 64, mean RSS total score declines from baseline were slightly greater in the U.S. patients. Similar findings are seen for each dosing regimen.

Table 55 Study CL201: RSS total score, change from baseline by region and regimen (ITT)

Visit	Subgroup	Q2W (N=26)		Q4W (N=26)		Overall (N=52)	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	US	17	1.85 (1.33)	19	1.66 (1.03)	36	1.75 (1.17)
	Non-US	9	2.06 (0.85)	7	1.71 (0.99)	16	1.91 (0.90)
Week 40	US	17	LS mean change (SE) (95% CI) -1.23 (0.13) (-1.48, -0.98)	19	LS mean change (SE) (95% CI) -0.79 (0.10) (-1.00, -0.59)	36	LS mean change (SE) (95% CI) -1.00 (0.09) (-1.17, -0.83)
	Non-US	9	-0.75 (0.12) (-0.99, -0.51)	7	-0.53 (0.21) (-0.95, -0.12)	16	-0.66 (0.12) (-0.88, -0.43)
Week 64	US	17	-1.20 (0.13) (-1.45, -0.95)	19	-0.93(0.10) (-1.13, -0.73)	36	-1.06 (0.08) (-1.22, -0.89)
	Non-US	9	-0.64 (0.10) (-0.83, -0.45)	7	-0.60 (0.19) (-0.98, -0.23)	16	-0.63 (0.10) (-0.82, -0.43)

LS mean and 95% CI for change from baseline per GEE model, which included visit, regimen, visit by regimen as factors, and RSS total score at baseline as a covariate, with exchangeable covariance structure
 Source: FDA's analysis

Based on the combined dosing regimen data, mean RSS total score declined from baseline to week 64 at each of the 9 study sites except site #150 (table below). One site with especially large improvements (#140, Shriners Hosp. St. Louis) has very extensive experience with pediatric XLH. It is unclear why this site had larger improvements although it is possible that this site had a larger study population and could enroll more patients that were more severe at baseline than other smaller sites.

Table 56 Study CL201: RSS total score, change from baseline at week 64 by study site (ITT)

Site #	Investigator	Site Location	Country	n*	RSS total score, mean change from baseline*
138	Carpenter	Yale Univ.	USA	16	-0.90
139	Portale	UCSF	USA	8	-0.94
140	Whyte	Shriners Hosp. St. Louis	USA	6	-2.17
141	Linglart	Hopital Bicetre, Paris	France	2	-0.25
148	Hogler	Birmingham Childrens	UK	2	-0.75
149	Padidela	Manchester	UK	5	-1.40
150	Boot	Groningen	Netherlands	4	+0.13
152	Van't Hoff	Great Ormond Hosp. London	UK	3	-0.50
156	Imel	Indiana Univ.	USA	6	-0.50

*data for Q2W and Q4W groups combined for each site
 Source: ADRSS

Data Quality and Integrity

Review of the study conduct and submitted data did not raise any concerns about data quality or integrity.

Efficacy Results – Secondary and other relevant endpoints

The following secondary and other relevant endpoint results presented below are intended to provide additional clinical information in a descriptive manner. The results are presented for each dosing regimen and for the combination of both dosing regimens.

RSS knee subscore

Overall, the RSS knee subscore decreased by 0.59 at Week 40 and by 0.65 at Week 64 from a baseline score of 1.20. Decreases are also seen for each dosing regimen.

Table 57 Study CL201: RSS knee subscore, change from baseline by regimen (ITT)

RSS knee score	Statistics	Q2W (N=26)	Q4W (N=26)	Overall (N=52)
Baseline	Mean (SD)	1.21 (0.68)	1.19 (0.60)	1.20 (0.64)
Week 40^a	Mean (SD)	0.58 (0.50)	0.65 (0.34)	0.62 (0.43)
	Change from Baseline^b			
	LS mean (SE) 95% CI	-0.63 (0.10) (-0.82, -0.43)	-0.55 (0.07) (-0.67, -0.42)	-0.59 (0.06) (-0.70, -0.47)
Week 64	Mean (SD)	0.50 (0.47)	0.60 (0.38)	0.55 (0.42)
	Change from Baseline^b			
	LS mean (SE) 95% CI	-0.70 (0.09) (-0.87, -0.53)	-0.61 (0.07) (-0.75, -0.46)	-0.65 (0.06) (-0.76, -0.54)
CI = confidence interval; GEE = generalized estimation equation; ITT = intent to treat; LS = least squares; Q2W = every 2 weeks; Q4W = monthly; RSS = Rickets Severity Score ^a Primary efficacy endpoint ^b LS mean and CI per GEE model, which included visit, regimen, visit by regimen as factors, and RSS knee score at baseline as a covariate, with exchangeable covariance structure. Source: CSR Table 14.2.1.1.1.1				

RSS wrist subscore

Overall, the RSS wrist subscore decreased by 0.31 at Week 40 and by 0.27 at Week 64 from a baseline score of 0.60. Decreases are also seen for each dosing regimen.

Table 58 Study CL201: RSS wrist subscore, change from baseline by regimen (ITT)

RSS wrist score	Statistics	Q2W (N=26)	Q4W (N=26)	Overall (N=52)
Baseline	Mean (SD)	0.71 (0.62)	0.48 (0.52)	0.60 (0.58)
Week 40^a	Mean (SD)	0.17 (0.24)	0.40 (0.32)	0.29 (0.30)
	Change from Baseline^b			
	LS mean (SE) 95% CI	-0.44 (0.05) (-0.53, -0.35)	-0.18 (0.06) (-0.29, -0.06)	-0.31(0.04) (-0.38, -0.2)
Week 64	Mean (SD)	0.31 (0.32)	0.35 (0.28)	0.33 (0.30)
	Change from Baseline^b			
	LS mean (SE) 95% CI	-0.30 (0.06) (-0.42, -0.19)	-0.24 (0.05) (-0.34, -0.13)	-0.27 (0.04) (-0.35, -0.19)

CI = confidence interval; GEE = generalized estimation equation; ITT = intent to treat; LS = least squares;
 Q2W = every 2 weeks; Q4W = monthly; RSS = Rickets Severity Score
^a Primary efficacy endpoint
^b LS mean and CI per GEE model, which included visit, regimen, visit by regimen as factors, and RSS wrist score at baseline as a covariate, with exchangeable covariance structure.
 Source: CSR Table 14.2.1.1.1.1

Radiographic Global Impression of Change (RGI-C) score

Overall, the mean RGI-C scores, based on comparisons of on-treatment wrist and knee X-rays to their baseline X-rays, were 1.56 and 1.57 at Weeks 40 and 64, respectively, i.e., about midway between +1 (“minimal healing”) and +2 (“substantial healing”) on this scale.

Table 59 Study CL201: RGI-C Score by regimen (ITT)

RGI-C	Statistics	Q2W N=26	Q4W N=26	Overall N=52
Week 40	LS mean (SE) 95% CI	1.66 (0.09) (1.48, 1.84)	1.47 (0.14) (1.20, 1.73)	1.56 (0.07) (1.40, 1.72)
	Difference (Q2W-Q4W) 95% CI	0.19 (-0.12, 0.51)		
Week 64	LS mean (SE) 95% CI	1.56 (0.11) (1.34, 1.78)	1.58 (0.11) (1.36, 1.80)	1.57 (0.08) (1.42, 1.72)
	Difference (Q2W-Q4W) 95% CI	-0.02 (-0.34, 0.29)		

LS mean, p-value and 95% CI per GEE model, which included visit, regimen, visit by regimen as factors, and RSS total score at baseline as a covariate, with exchangeable covariance structure
 Source: CSR Table 14.2.1.2.1.1

The higher-baseline-RSS group (n=34) showed the greatest improvements in RGI-C score (mean 1.98 at Week 64), but the lower-baseline-RSS group also displayed some apparent modest improvement in RGI-C score (mean 0.80 at week 64).

Reviewer Comment:

RGI-C scores, like RSS total scores, improved more in the patients with the worst rickets, for the same reason: more severe abnormalities at baseline created more opportunity for improvement.

RGI-C knee subscore and wrist subscore

As was seen in the RSS knee subscore and wrist subscore results (see above), the RGI-C score also indicated improvements in the knee and wrist (positive scores reflect improvement relative to baseline).

Table 60 Study CL201: RGI-C Knee Subscore and Wrist Subscore by regimen (ITT)

Visit	Parameter	Statistics	Q2W (N=26)	Q4W (N=26)	Overall (N=52)
Knee Score	Week 40	LS mean (SE) 95% CI	1.60 (0.11) (1.39, 1.80)	1.34 (0.15) (1.05, 1.63)	1.47 (0.09) (1.29, 1.64)
	Week 64	LS mean (SE) 95% CI	1.57 (0.10) (1.37, 1.77)	1.53 (0.10) (1.34, 1.73)	1.55 (0.07) (1.41, 1.69)
Wrist Score	Week 40	LS mean (SE) 95% CI	1.63 (0.15) (1.35, 1.92)	1.46 (0.13) (1.20, 1.71)	1.54 (0.10) (1.36, 1.73)
	Week 64	LS mean (SE) 95% CI	1.65 (0.15) (1.35, 1.95)	1.55 (0.12) (1.30, 1.79)	1.60 (0.10) (1.40, 1.79)

LS mean and 95% CI per GEE model, which included visit, regimen, visit by regimen as factors, and RSS knee score/wrist score at baseline as a covariate, with exchangeable covariance structure
 Source: CSR Table 14.2.1.2.1.1, Table 14.2.1.2.1.1

In addition to the RGI-C scores, the specific radiographic abnormalities assessed (metaphyseal lucency, metaphyseal/epiphyseal separation, metaphyseal fraying and metaphyseal concavity) each showed improvement from baseline in the majority of patients, including within the lower-baseline-RSS group.

Lower extremity deformity: RGI-C long leg scores

Lower extremity deformities, as assessed by RGI-C scores of standing long leg radiographs (i.e., changes in genu varum [bowing of the legs] and genu valgum [knock knees]), showed a modest improvement from baseline to Week 64, with LS mean values of 0.47, 0.57 and 0.30 for the overall study population, higher-RSS and lower-RSS patients respectively. There were 36/52 (69%) patients with long-leg RGI-C > 0 (improvement) and 3/52 (5.8%) patients with long-leg RGI-C < 0 (worsening). Respective improvements from baseline were observed in 27% and 36% of abnormal left and right femurs; 25% and 22% of abnormal left and right tibiae; and 19% and 20% of abnormal left and right fibulae.

Reviewer Comment:

Improvements in deformities were small, but it is likely that a longer treatment duration would be necessary for demonstrating large improvements in deformities, if they exist.

Growth

Growth was significantly impaired in the study population at baseline, with mean standing height percentile of 8.7 and mean height Z-score of -1.89 for all patients. At week 64, mean height increased from baseline by 7.2 cm, mean height percentile increased by 2.0 and mean height Z-score increased by 0.15, with somewhat larger increases in the Q2W group (table and figure below). Mean height Z-score increase was similar between boys and girls (0.14 and 0.17 respectively), and between higher-RSS and lower-RSS patients (0.17 and 0.13 respectively). Growth velocity was also assessed, using growth data from the 2 years before enrollment compared to data on study. In the overall study population, mean growth velocity increased from 5.35 cm/year pre-enrollment to 5.91 cm/year on treatment.

Table 61 Study CL201: Percentile of Standing Height, Standing height Z-score and Growth Velocity, change from baseline at week 64 by regimen (ITT)

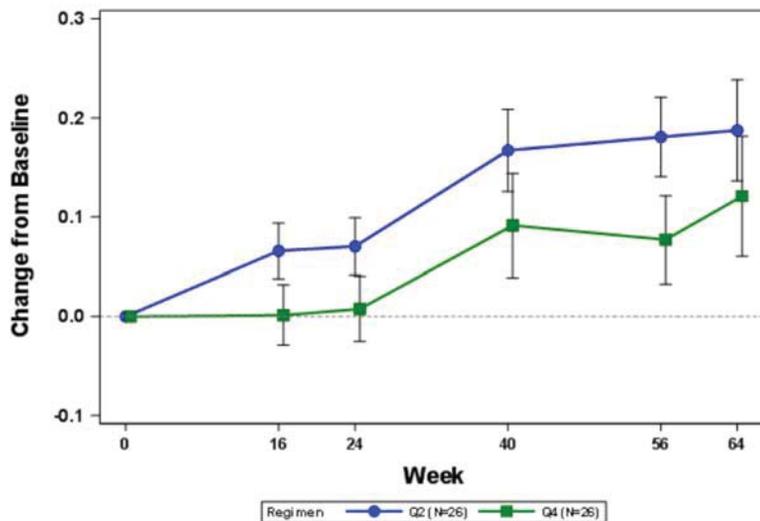
Growth Endpoint	Statistics	Q2W (N=26)	Q4W (N=26)	Overall (N=52)
Percentile of standing height				
Baseline	Mean (SD)	11.1 (13.8)	6.2 (8.2)	8.7 (11.5)
Change from baseline	Mean (SD)	3.9 (4.9)	0.2 (3.7)	2.0 (4.7)
Standing height Z-score				
Baseline	Mean (SD)	-1.72 (1.03)	-2.05 (0.96)	-1.89 (1.00)
Change from baseline ^a	LS mean	0.19 (0.05)	0.12(0.06)	0.15 (0.04)
	95% CI	(0.09, 0.29)	(0.00, 0.24)	(0.08, 0.23)
Growth velocity				
Baseline (cm/year)	Mean (SD)	5.45 (1.17)	5.24 (1.40)	5.35 (1.28)
Change from baseline	Mean (SD)	0.73 (1.40)	0.37 (2.16)	0.55 (1.80)
	95% CI ^b	(0.15, 1.30)	(-0.54, 1.28)	(0.03, 1.07)

^a LS mean change from baseline and 95% CI per GEE model, which included visit, regimen, visit by regimen and gender as factors, age and standing height Z score as covariates, with exchangeable covariance structure

^b CI is obtained from one sample T-test

Source: CSR Table 14.2.1.3.7.1, Table 14.2.1.3.4.1 and Table 14.2.1.3.1.1

Figure 36 Study CL201: Standing height Z-score change from baseline (LS mean \pm SE) by dose regimen (ITT)



Source: CSR Fig. 11.2.1

Reviewer Comment:

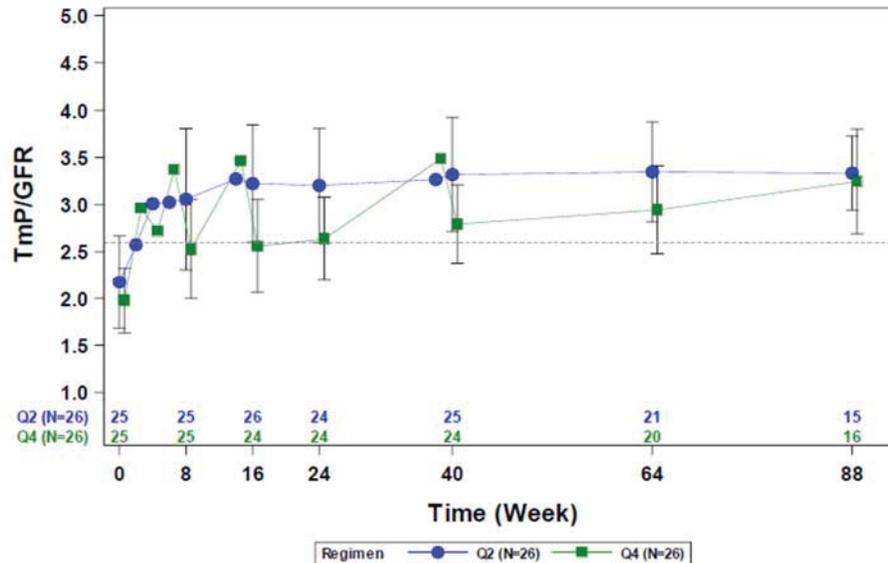
In the absence of controls, the significance of these small changes in growth parameters is unclear. The growth velocity data are particularly difficult to interpret because of the use of retrospective data, and because a comparison of pre- and post-enrollment data (without a control group) would rely on an assumption of constant background growth velocity. However, the greater height increases seen in the Q2W versus Q4W patients are consistent with trends in the various rickets and PD parameters; therefore, might be considered to provide a dose-response comparison. There was also greater response in higher-RSS versus lower-RSS patients with respect to growth velocity (consistent with changes in RSS scores). Although improvement in height Z-score was similar between higher-RSS and lower-RSS patients at week 64, higher-RSS patients showed greater improvement at week 88 (see below).

Secondary PD endpoints

TmP/GFR

TmP/GFR increased during treatment, demonstrating the improvement in renal phosphate wasting (figure below). In the Q2W group, mean TmP/GFR increased from 2.2 mg/dL at baseline to 3.3 mg/dL at weeks 40-64 (LLN \approx 2.6 mg/dL). In the Q4W group, mean TmP/GFR was 3.5 mg/dL at week 38 (midpoint of dose interval), and lower at the ends of dosing intervals (at weeks 40 and 64, 2.8 and 3.0 mg/dL respectively) but remaining above LLN.

Figure 37 Study CL201: Serum TmP/GFR mean (SD) level (mg/dL) by regimen/visit (PK/PD Analysis Set)

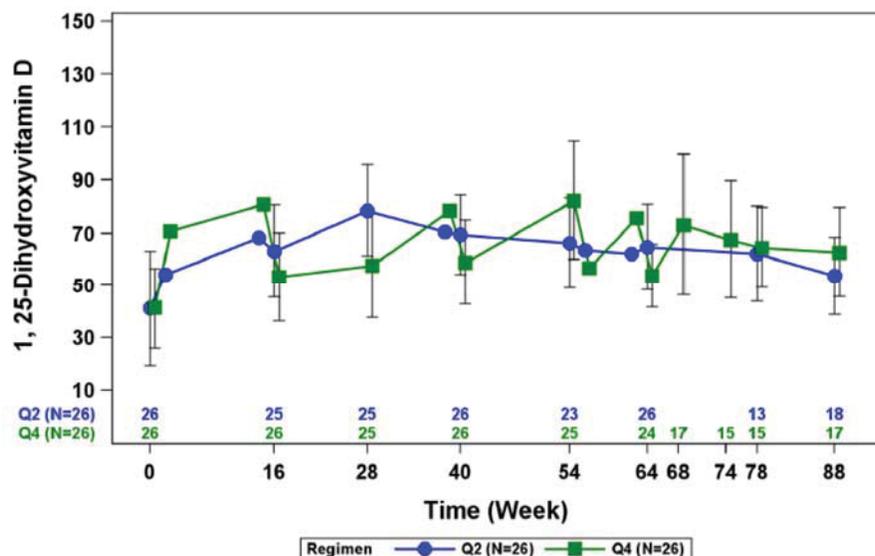


Source: Fig. 14.2.3.3.1.99, submitted on 1/17/18 Dotted line = LLN (2.6 mg/dL)

Serum 1,25(OH)₂D

Dihydroxyvitamin D increased during treatment, consistent with increased 1- α -hydroxylase activity. In the Q2W group, mean 1,25(OH)₂D level increased from 41.3 pg/mL at baseline to 78.8, 69.6 and 64.9 pg/mL at weeks 28, 40 and 64 respectively, indicating an initial increase followed by a slight downward trend over time (figure below). In the Q4W group, 1,25(OH)₂D levels declined at the ends of dosing intervals. In both groups after dose was stabilized, 1,25(OH)₂D levels were generally in the normal range (which is approx. 18-72 pg/mL) and above pre-treatment baseline.

Figure 38 Study CL201: Serum 1,25(OH)₂D mean(SD) level (mg/dL) by regimen/visit (PK/PD Analysis Set)



Source: Fig. 14.2.3.2.1.99, submitted on 1/17/18

Serum alkaline phosphatase (ALP) and bone-specific alkaline phosphatase (BALP)

At baseline, mean (SD) serum ALP was 459 (105) U/L (overall study population), above the ULN for children age 5-12 years old (which is estimated at 297 to 385 U/L, depending on age/sex, and is shaded in Figure 39, below). At week 40, mean level declined to 395 U/L (-13%); at week 64, mean level declined further to 369 U/L (-20%), i.e. near the ULN. Declines were slightly greater in the Q2W group at most points. Within the Q2W group, the mean levels at baseline, week 40 and week 64 were 462, 382 and 354 U/L respectively.

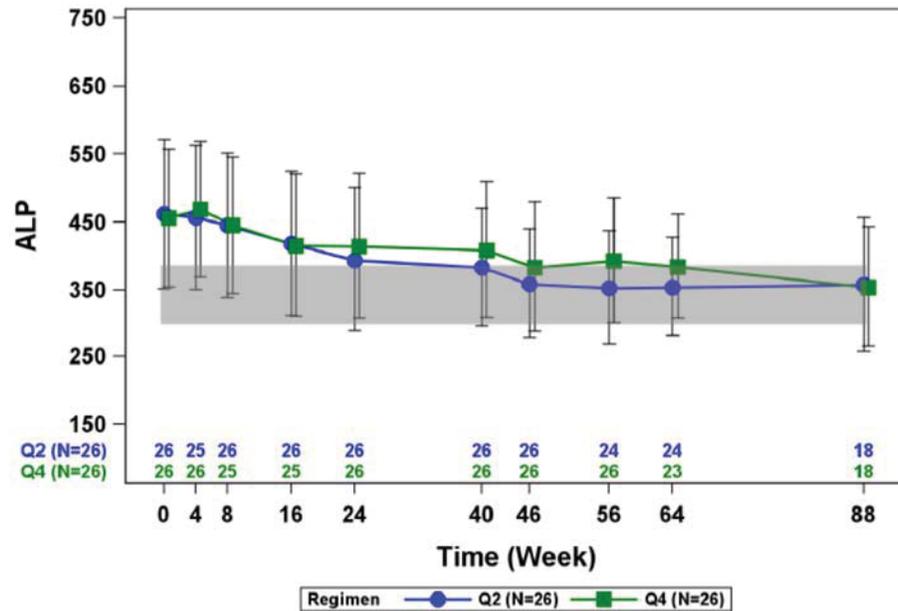
At baseline, mean (SD) serum BALP was 165 (52) mcg/L, well above the ULN for children this age which was estimated at 23 mcg/L. At week 40, mean level declined to 134 mcg/L (-17%); at week 64, mean level declined further to 115 mcg/L (-29%), but remained markedly above normal for age group (Figure 40, below).

Higher-RSS patients (n=34), compared to lower-RSS (n=18), had higher baseline ALP (mean 497 vs. 388 U/L), and larger declines with treatment, particularly with Q2W dosing.

Reviewer Comment:

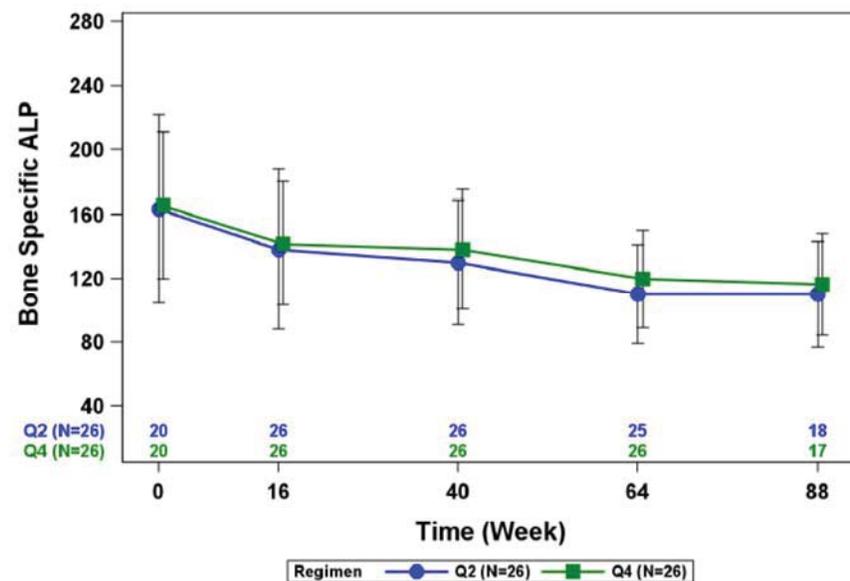
These data support the concept that ALP and BALP are markers of rickets activity in XLH patients and support the findings from other burosumab pediatric efficacy data.

Figure 39 Study CL201: Serum ALP, mean (SD) level (U/L) by regimen/visit (PK/PD Analysis Set)



Grey bar indicates the ULN ranges, approx.. 297 to 385 U/L, depending on age/sex of the child
 Source: Fig. 14.2.3.4.1.99, submitted on 1/17/18

Figure 40 Study CL201: Serum BALP, mean (SD) level (mcg/L) by regimen/visit (PK/PD Analysis Set)



Source: Fig. 14.2.3.4.1.99, submitted on 1/17/18

Serum P1NP and CTX

P1NP and CTX, markers of bone formation and resorption respectively, increased during the study. Mean serum P1NP increased from 791 ng/mL at baseline to 1033 and 931 ng/mL at weeks 40 and 64 (increases of 37% and 20% respectively). Mean serum CTX increased from 2.16 ng/mL at baseline to 2.98 and 3.09 ng/mL at weeks 40 and 64 (increases of 43% and 50% respectively).

Reviewer Comment:

The applicant interprets the increased bone turnover as evidence of improvement in osteomalacia, with replacement of excess osteoid by normally mineralized bone. Although this seems plausible, there is insufficient evidence to support the use of these markers as efficacy parameters (b) (4)

Dose/Dose Response

Because dose was titrated in individual patients according to serum phosphorus level, this study does not provide a comparison of different doses for efficacy response.

Durability of Response

In addition to week 64 data on all CL201 patients, the BLA includes week 88 data on the first 36 (“pre-expansion”) patients. As discussed above, mean burosumab Q2W dose reached a plateau of ~1 mg/kg at around weeks 40-64 of the study, then declined slightly. Mean serum phosphorus was maintained in the low-normal range for age through week 88, with no apparent downward trend, and TmP/GFR indicated that improvement in renal phosphate wasting also did not diminish over time. Serum 1,25(OH)₂D levels declined slightly from a peak at week 28 to later timepoints, but remained in normal range and above baseline.

As outlined above, improvements from baseline in RSS total scores and subscores were virtually unchanged between weeks 40-64. Among the 36 pre-expansion patients, week 88 RSS scores showed little further change (table below). Similar to previous timepoints, the declines from baseline in RSS total score were confined to higher-baseline-RSS patients (mean change from baseline at week 88 = -1.26, versus +0.14 in lower-RSS patients). Mean RGI-C Global Score at week 88 was +1.65 and mean RGI-C score for lower extremity deformity at week 88 was +0.52; both of these values were slightly increased from week 64.

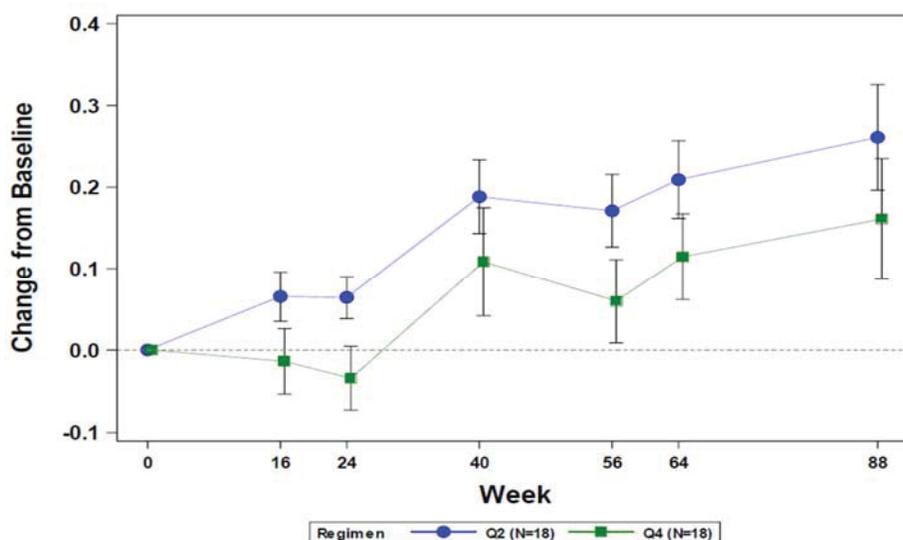
Table 62 Study CL201: RSS total score, mean change from baseline by dose regimen (pre-expansion patients)

	Q2W n=18	Q4W→Q2W‡ n=18	Overall n=36
Baseline , mean	1.53	1.33	1.43
Week 40 , mean	0.86	1.14	1.00
Mean change from baseline	-0.67	-0.19	-0.43
Week 64 , mean	0.75	1.00	0.88
Mean change from baseline	-0.78	-0.33	-0.56
Week 88 , mean	0.94	0.82	0.89
Mean change from baseline	-0.58	-0.50	-0.54

‡Q4W patients were dosed Q4W until week 64, then switched to Q2W dosing
 Source: ADRSS and UX023-CL201 Ad Hoc Analysis Table 14.2.1.1.1.2

Small improvements in growth continued between week 64 and 88 among the 36 pre-expansion patients. Mean height increased during this 24-week interval by 2.8 cm and 2.6 cm in continuous-Q2W and Q4W-to-Q2W groups respectively, and height Z-scores continued to increase in both groups (figure below). These further improvements at week 88 occurred mainly in the higher-RSS group, in which the LS-mean increase from baseline to week 88 in height Z-score was 0.29, compared to 0.13 in the lower-RSS group. Mean growth velocity from baseline to week 88 was increased by 0.29 cm/year from pre-baseline among the 36 pre-expansion patients, which was unchanged from the baseline-to-week 64 period.

Figure 41 Study CL201: Standing height Z-score change from baseline (LS mean ± SE) by dose regimen (pre-expansion patients)



Source: UX023-CL201 Ad Hoc Analysis Fig. 14.2.1.3.1.2

Reviewer Comment:

These data show no evidence of a loss of effect of the drug over time in children. However despite near-normalization of serum phosphorus, rickets scores did not continue to improve after week 40, so that rickets did not completely disappear in most children (mean RSS total score at week 88 = 0.89, down from 1.43 at baseline among pre-expansion patients) and growth deficits persisted (mean height Z-score -1.7, improved from -1.9 at baseline). Thus, long-term clinical outcomes in terms of skeletal abnormalities remain uncertain.

Persistence of Effect

Because all patients have continued in this study, there is no information on the effects of stopping burosumab treatment in children. It is highly unlikely that as a monoclonal antibody, burosumab would continue to have an effect on bone once treatment is halted.

8.1.2. Study UX023-CL002

Study title: A Retrospective Longitudinal Study of Skeletal Outcomes in Children with X-linked Hypophosphatemia (XLH)

Overview and Objective

The primary objective of this study is to characterize change in rickets severity over time with conventional therapy (oral phosphate/active vitamin D) in children with XLH ages 5 to 14 years. The secondary objective is to characterize the effects of conventional therapy on other skeletal outcomes, particularly lower extremity deformities and growth. The data were primarily intended for comparison to the uncontrolled phase 2 study of children age 5-12 years with XLH (study CL201).

Study Design

This study is a non-interventional, retrospective review of data from pediatric XLH patients receiving conventional therapy, conducted at four centers with expertise in XLH. Each site accessed the radiographs and medical records of their patients age 5-14 years old with XLH who met eligibility criteria and provided consent. De-identified x-rays were sent to the [REDACTED] (b) (4) [REDACTED] the central imaging facility also used in study CL201, for interpretation. Other historical data gathered included demographics, family history, history of XLH diagnosis and treatment, relevant co-morbid conditions, growth data and biochemical markers of phosphate metabolism.

Study Population

For inclusion in the study, patients could be male or female, with XLH diagnosis based on confirmed *PHEX* mutation in the patient or a directly related family member with appropriate

X-linked inheritance, or a clinical diagnosis of XLH based on biochemical profile and clinical symptoms. Patients must have had radiographic images from at least two time points between the ages of 5 and 14 years, inclusive. Patients who subsequently enrolled in study CL201 were not eligible.

Study Endpoints

RSS and RGI-C: In order to provide comparison to study CL201, this study used these same radiographic endpoints of rickets severity, which require bilateral wrist and knee x-rays (see section 8.1.1). In order to approximate the intervals between paired images in study CL201 (40 and 64 weeks), x-ray pairs that had been taken approximately 1-2 years apart were analyzed for RSS and RGI-C endpoints in this study. The RSS and RGI-C raters scored x-rays from this study and from week 64 of study CL201 in random order in order to keep them blinded to the treatment status of the patient. As in study CL201, there is one RSS reader [REDACTED] (b) (4), and three RGI-C readers (academic pediatric radiologists) whose scores are averaged for analyses. Paired standing long leg x-rays were also given RGI-C scores for deformities by these readers, as in study CL201.

Growth: standing height was derived from available records, and as in study CL201, endpoints included height in cm and age/sex based Z-score and percentile.

Biochemical parameters: endpoints included change over time in serum phosphorus, calcium, iPTH, 1,25(OH)₂D and ALP, corresponding to dates close to the dates of x-rays where available.

Statistical Analysis Plan

Analysis Population

Full Analysis Set: All enrolled subjects who meet the inclusion and exclusion criteria, and have been treated with conventional therapy.

Radiograph Analysis Set: All subjects in the Full Analysis Set who had a pair of bilateral wrist and knee images taken 1-2 years apart (± 3 months) between the ages of 5 and 14 years.

Statistical Methods

Descriptive statistical analyses were conducted for this retrospective study. Continuous variables were summarized with means and standard deviations. 95% Confidence Intervals (C.I.s) were calculated for selected continuous variable summary using one sample t test. Categorical variables were summarized by counts and by percentages of subjects in corresponding categories. No formal hypothesis testing was performed. No imputation of missing data was made, unless stated otherwise.

RSS scores were summarized as both continuous and categorical variables for

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wrist, knee and total scores separately. Change in RSS scores between paired radiographic images was summarized as both continuous and categorical variable. Number and percentage of data with at least 1 score reduction in RSS total scores was calculated.

RGI-C scores of paired radiographic images were summarized as continuous variable for wrist, knee and global scores separately. Categorical analysis was performed for RGI-C scores in different ranges: [-3, -2), [-2, -1), ..., [1, 2) and [2, 3], where the category of [2, 3] represents RGI-C response.

Analysis of growth endpoints was performed on full analysis set and repeated for radiograph analysis set. The standing height (length) was summarized by year of age in cm, Z score and percentile. Overall summary across all age years were performed on Z score and percentile only.

The descriptive summary of XLH biochemical endpoints was performed on full analysis set and repeated for radiograph analysis set.

Protocol Amendments

The original protocol was dated 5/12/2015 and amendment 1 dated 9/25/2015. Several changes were made in order to narrow the scope of the study, from a broad historical reference study of pediatric XLH, to a focus on rickets and other skeletal outcomes in children age 5-14 years old receiving conventional therapy.

Study Results

Compliance with Good Clinical Practices

The applicant attests that study CL002 has been conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

Study CL002 is among the covered clinical studies, as defined by 21 CFR 54.2(e), which provide the primary evidence establishing the effectiveness and safety of burosumab (see Appendix 15.2). The applicant has adequately disclosed financial interests/arrangements with the clinical investigators as recommended in FDA guidance, and no concerns are raised about the integrity of the data.

Patient Disposition

Four clinical sites with expertise in XLH participate in this study:

- Shriner's Hospital, St. Louis (Michael Whyte MD, site #140)
- Children's Hospital of Los Angeles (site #142)
- Shriner's Hospital, Montreal (site #173)
- Bicetre Hôpital, Paris, France (site #141)

As of the cutoff date for the interim report (8/9/16), there were 52 patients enrolled (39 from site #140, and 13 from site #142), constituting the Full Analysis Set. Among these there were 35 patients who, while receiving conventional therapy, had wrist and knee radiographs taken 1-2 years apart between the ages of 5-14 y/o, and constituted the Radiographic Analysis Set (RAS). These 35 patients had been followed in a separate prospective, longitudinal observational study of children with XLH conducted by Dr. Whyte (site #140), in which bilateral wrist and knee radiographs were taken at 1-2 year intervals as part of the study protocol, regardless of clinical status. These 35 children contributed a total of 60 paired radiographic images of wrists and knees, with a mean time of 1.7 years between the baseline and post-baseline image within each pair; and a total of 20 paired standing long leg images.

The applicant was informed by the investigators that conducting radiographs at 1-2 year intervals was not common practice in this population; therefore, no such data from the other 3 sites were available.

Demographic and Baseline Characteristics

In the Radiographic Analysis Set (RAS), 24/35 (69%) of patients were female, 34/35 (97%) were white and 30/35 (86%) were non-Hispanic. The mean age at the time of the baseline paired radiograph was 8.6 years, similar to study CL201 baseline (mean 8.5 years). The age at which conventional therapy had been initiated (mean 2.2 years old, range 0.3-9.3) was also similar to patients in study CL201 (mean 2.1 years old, range 0.0-5.7). The duration of conventional therapy prior to baseline radiographs was >6 years, also similar to study CL201. Mean RSS scores (for the earlier radiograph pair for each patient) were 1.40 (total), 0.43 (wrist) and 0.96 (knee), which were somewhat lower than baseline RSS in study CL201. Mean height Z-score was 1.89, the same as study CL201.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All patients in the RAS were receiving oral phosphate and calcitriol at the time of the baseline and post-baseline radiograph sets, and reported no interruptions in treatment of >3 months; there were no reports of noncompliance.

Efficacy Results

RSS

Among the 60 pairs of matching baseline and post-baseline radiographs, 13 pairs showed fused growth plates on the latter images, precluding calculation of change in RSS (these were mostly

from patients age 13-14 years old). Analysis of the 47 other radiograph pairs showed that mean (SD) total RSS decreased from 1.33 (0.75) for the baseline radiographs to 1.17 (0.89) for post-baseline, a mean change of -0.16 (12% reduction). There were similar small declines in RSS wrist and knee subscores. Confidence intervals for all of these changes from baseline include zero.

As in study CL201, RSS changes were highly dependent on baseline RSS. In 25 paired radiographs where the baseline RSS was ≥ 1.5 , mean (SD) RSS total score declined from 1.88 (0.55) at baseline to 1.42 (0.85) at post-baseline. In 22 paired radiographs where the baseline RSS was < 1.5 , mean (SD) RSS increased from 0.70 (0.33) to 0.89 (0.87).

RGI-C

Because RGI-C rickets scores do not require open growth plates, all 60 pairs of wrist/knee radiographs were evaluable. The mean RGI-C global score was +0.79 for the overall group, +0.85 for the higher RSS subgroup (n=32) and +0.69 for the lower RSS subgroup (n=24). The mean RGI-C subscores in the overall group for wrist and knee were +0.62 and +0.78 respectively. The threshold for "substantial healing" (RGI-C global score $\geq +2$) was met by 17% of patients (16% and 17% of higher- and lower-RSS groups).

Lower extremity deformity

Among the 35 RAS patients, there were 30 available pairs of standing long leg radiographs. At baseline, 80-100% had deformities, predominantly genu varus (bowing of the leg). After a mean time of 1.9 years between baseline and post-baseline images, the mean RGI-C lower limb deformity score was +0.35 for the overall group, +0.48 for higher-RSS patients and +0.29 for lower-RSS patients. There were 4 radiograph pairs (20%) with scores of +1 to +2, and none with scores $> +2$.

Growth

During the time intervals corresponding to the 60 radiograph pairs (mean 1.7 yr), there were no changes in height Z-score (mean at baseline and post-baseline = -1.89 and -1.89) or height percentile (7.8 and 8.0).

The study report also presents growth data for the Full Analysis Set of 52 children treated with conventional therapy at ages 1-13 years old. For both boys and girls, mean height remained near or below the 5th percentile for CDC reference data (CSR, Figures 14.2.1.3.1 and 14.2.1.3.2).

Biochemistry parameters

Mean serum phosphorus was 2.8 mg/dL at the time of the 60 baseline radiographs, and 2.9 mg/dL at the time of the 60 post-baseline radiographs. This is below the designated LLN in this population (3.2 mg/dL), but above the mean baseline level in study CL201 (2.33 mg/dL), which may reflect ongoing therapy with oral phosphate/calcitriol (which had been withdrawn prior to study CL201 baseline).

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Mean serum alkaline phosphatase (ALP) was 443 and 420 U/L at the time of baseline and post-baseline radiographs respectively (both above normal range). Serum calcium and iPTH levels showed minimal change. Serum 1,25(OH)₂D levels were not assessed because there were very few measures of this parameter.

Comparison of conventional therapy to burosumab

As noted above, the patients in this study CL002 were generally similar to the study CL201 population, but were more likely to be female (69% vs. 54%) and had less severe rickets (mean total RSS 1.4 vs. 1.8). In study CL201, burosumab was associated with larger RSS declines in girls compared to boys, and in higher-RSS vs. lower-RSS patients. Therefore, the differences in study populations between CL201 and CL002 in sex and baseline RSS may confound the efficacy comparisons. In order to address these imbalances, the applicant compared these studies using Propensity Score matching; these analyses are reviewed below in section 8.2.1.

8.1.3. Study UX023-CL205

Study title: 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) (Amendment 1)

Overview and Objective

This is the first study of burosumab in children with XLH age 1-4 years old. The primary objectives of this ongoing study are to establish the safety profile of burosumab and determine the effects on PD markers of phosphate homeostasis in this age group. Additional objectives are to assess the effects on rickets, growth and lower extremity deformity; and pharmacokinetics. The week-24 data were submitted in the original BLA; the week-40 data, including radiographic efficacy data, were submitted on 10/27/2017 (SD-10).

Study Design

The study was planned to enroll ~10 children age 1-4 years with clinical findings consistent with XLH, including hypophosphatemia and radiographic rickets. The study is single-arm: all patients are treated with burosumab at a starting dose of 0.8 mg/kg Q2W. One dose adjustment, to 1.2 mg/kg Q2W, is allowed at any time if serum phosphorus increases by <0.5 mg/dL from baseline, and two consecutive measures are below LLN (unless a dose was missed). Dosing is to be withheld if serum phosphorus increases above ULN for age. SC injections are administered to the abdomen, upper arms or thighs, with rotation of site at each injection. The duration of treatment is 64 weeks, with an extension planned.

Similar to study CL201, clinic visits occur at approx. 4-week intervals for the first 24 weeks and at 8-week intervals thereafter, with home visits intervening every 2 weeks. Schedules of efficacy and safety labs are also similar to CL201. Growth is recorded about every 12 weeks.

Renal ultrasound and skeletal X-rays (knee, wrist, standing long leg) and renal ultrasound are conducted at screening/baseline, weeks 40 and 64. Radiograph collection is coordinated by the same contractor as study CL201 (b) (4) and rickets scoring by the same radiologists (b) (4) for RSS, 3 independent readers for RGI-C) using the same methodology.

Study population

Study CL205 enrolled Male/Female children age 1-4 inclusive, with clinical findings consistent with XLH including hypophosphatemia (<3.0 mg/dL), radiographic evidence of rickets (at least 5 subjects with an RSS at the knee of ≥ 1.5 at screening), and a confirmed *PHEX* mutation or variant of uncertain significance (VUS). There were exclusions for nephrocalcinosis grade 4 (stone formation); elevated serum creatinine for age; hypo- or hypercalcemia; or planned orthopedic surgery. Any treatments of oral phosphate or active vitamin D were to be stopped with a 7-day washout. Also prohibited were growth hormone, AIOH antacids, thiazides, or bisphosphonates. Vitamin D supplements were to be provided if serum 25(OH)D levels fall below 20 ng/mL.

Study Endpoints

Primary efficacy endpoint: serum phosphorus (change from baseline)

Serum phosphorus was measured about every 2-4 weeks for the first 24 weeks, then every 8 weeks. Because serum phosphorus is subject to diurnal and postprandial variation, samples were collected after a minimum overnight fast of 4 hours. Samples were analyzed at a central lab (b) (4).

Secondary efficacy endpoints (see detailed discussion of these endpoints in study CL201 above)

- RGI-C Global Score at weeks 40 and 64
- RSS total score, change from baseline at weeks 40 and 64
- Lower extremity skeletal abnormalities, including genu varum and genu valgus, by RGI-C long leg score at weeks 40 and 64
- Recumbent length (patients <2 y/o or unable to stand for the measurement) or standing height, changes from baseline in height Z-score and percentile; historical growth records may be used to evaluate change in growth velocity
- Serum alkaline phosphatase (ALP), change and % change from baseline

Other efficacy endpoints

- Serum 1,25(OH)D and urine phosphorus, change from baseline
- RGI-C wrist and knee subscores at weeks 40 and 64
- RSS wrist and knee subscores, change from baseline at weeks 40 and 64

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Safety endpoints

- AEs including events of interest (Injection site reaction, immunogenicity, hyperphosphatemia, ectopic mineralization, restless leg syndrome)
- Vital signs, weight
- Laboratory including serum Ca, iPTH, 25(OH)D, urine Ca and creatinine, FGF23 level
- Anti-burosumab Ab
- ECG
- Renal ultrasound to assess potential nephrocalcinosis

Reviewer Comment:

Because of the younger age of study patients, some assessments that are included in study CL201 (6MWT, POSNA-PODCI, echocardiograms) are not conducted in this study.

Statistical Analysis Plan

The following statistical analyses are specified in the statistical analysis plan.

Sample size

The study planned to enroll approximately 10 pediatric patients between 1 and 4 years old. To maintain balance by gender, no more than 7 subjects of either gender would be enrolled.

Interim Analysis

The primary analysis was planned at Week 40. Additional efficacy and safety analyses were conducted at Week 64. A Week 24 analysis was planned as an administrative analysis to support regulatory interaction.

Analysis Population

- Efficacy Analysis Set: all subjects who received at least one dose of study drug and have at least one post-study drug measurement of serum phosphorus.
- Safety Analysis Set: all subjects who received at least one dose of study drug.
- Pharmacokinetic (PK) and Pharmacodynamic (PD) Analysis Set: all subjects who received at least one dose of study drug and had evaluable blood samples.

Statistical Methods

Descriptive statistics were provided for the observed serum phosphorus value, its change from Baseline, and its percent change from baseline at each visit. A GEE model was used to analyze the by-visit change from baseline with baseline serum phosphorus measure as covariate and visit as factor in the model. The proportion of subjects reaching the normal range (3.2-6.1 mg/dL) were reported. The percentage of time a subject remained within the serum phosphorus normal range was also summarized.

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Reviewer Comment:

When only one visit (Week 40) was included in the GEE model for the primary analysis, the model was exactly an ANCOVA model with baseline value as covariate.

Descriptive statistics for all RGI-C scores and RSS scores were provided in both continuous and categorical summary. GEE models were used to analyze RGI-C scores and change from baseline in RSS scores for Week 40 and 64. The RGI-C responder rate was calculated. Summary of abnormality at baseline and change in abnormality at Week 40 and Week 64 were also presented.

Growth in standing height/recumbent length and weight were summarized over time in observed value, Z-score and percentile.

Protocol Amendments

The original protocol (dated 10/22/15) proposed a starting dose of 0.3 mg/kg Q2W for two doses and a target dose of 0.6 mg/kg Q2W. Based on additional PK/PD data from study CL201 and extrapolation to younger patients, protocol amendment 1 (3/28/16) increased the starting dose to 0.8 mg/kg Q2W (prior to initiating the study), and made several other changes. None of these changes altered the primary efficacy endpoint or key safety monitoring in this trial.

Study Results

Compliance with Good Clinical Practices

The applicant attests that study CL205 has been conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

Study CL205 is among the covered clinical studies, as defined by 21 CFR 54.2(e), which provide the primary evidence establishing the effectiveness and safety of burosumab (see Appendix 15.2). The applicant has adequately disclosed financial interests/arrangements with the clinical investigators as recommended in FDA guidance, and no concerns are raised about the integrity of the data.

Patient Disposition

A total of 13 children are enrolled in this study at 3 centers: Yale Univ. (#138, PI-Thomas Carpenter, n=8); Shriners Hosp. St. Louis (#140, PI-Michael Whyte, n=3) and Indiana Univ. (#156, PI-Erik Imel, n=2). All children completed week 40 assessments; none had discontinued as of the cutoff date, which was 4/20/17 for the week 40 report.

Protocol Violations/Deviations

Three patients had one major protocol deviation each, but none that would significantly impact study results.

Demographic and other baseline characteristics

Sex: 9 (69%) males; 4 (31%) females
Age: mean (SD): 2.9 (1.15) years; range: 1.2 to 4.9 years
Race: 12 (92%) White; 1 (8%) Black or African-American
Ethnicity: 11 (85%) not Hispanic or Latino; 2 (15%) Hispanic or Latino

At baseline, mean (SD) serum phosphorus was 2.51 (0.28) mg/dL (reference range for age group ~3.2-6.1 mg/dL). Most subjects (11/13) were positive for known pathogenic *PHEX* mutations; one patient had a variant in the *PHEX* gene considered likely pathogenic, and one patient had a variant of unknown significance.

All 13 patients had received conventional therapy with oral phosphate and active vitamin D analogs before enrolling in the study, with a mean (SD) duration of 16.9 (14.4) months, and mean (SD) age at initiation of 20.9 (18.2) months. Despite this early initiation of treatment, all patients had rickets, with RSS scores >0 at both the knee and the wrists. Mean (SD) RSS scores were 2.92 (1.37) overall; 1.65 (0.80) at the knee and 1.27 (0.70) at the wrist. Metaphyseal abnormalities were noted on radiographs in all subjects at the distal femur and in most subjects at the proximal tibia, the distal ulna, and the distal radius. All patients had genu varum in both femurs and in both tibiae. Patients had histories of knee deformity (62%); bone deformity, skull malformation, and gait disturbance (54%); tibial torsion and body height below normal (46%); foot deformity (38%); and tooth abscess (31%). Serum ALP was elevated in 11/13 subjects (85%), with a mean (SD) of 549 (194) U/L (ULN is ~297 to 345 U/L). Growth was impaired at baseline: mean (SD) recumbent length/standing height was 89.2 (7.6) cm, mean (SD) percentile for age and sex was 18.0% (25.26%), and mean (SD) Z score was -1.38 (1.20).

Reviewer Comments:

Compared to study CL201, patients were more likely to be male (69% versus 46%), which is not consistent with the higher prevalence of XLH in females due to X-dominant inheritance. The proportion of patients with identified-pathogenic PHEX mutation was similar (85% versus 87% in studies CL205 and CL201). Conventional therapy was initiated at an early age in both studies (mean 1.6 and 2.1 years old). Although it was intended that study CL205 would enroll some treatment-naïve (to conventional therapy) patients, this did not occur.

Baseline serum phosphorus was slightly higher than study CL201 (mean 2.51 versus 2.33 mg/dL), which may partly reflect the younger age of the patients. Serum ALP was also higher (mean 549 versus 459 U/L), which also may be mainly a function of age. Despite the more limited duration of disease activity in younger patients, rickets was at least as severe (RSS mean

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total score 2.92 versus 1.80 in study CL201), with high prevalence of bowing and other deformities, and significant growth impairment.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All 13 patients received all planned doses of burosumab at a prescribed dose of 0.8 mg/kg Q2W through Week 20, and 10 subjects continued to receive burosumab at 0.8 mg/kg Q2W through the data cutoff date (at least Week 40). Three subjects had undergone dose increases to 1.2 mg/kg Q2W based on the protocol-specified dose adjustment criterion (at Week 22 for 2 subjects and at Week 34 for 1 subject); burosumab dose continued at the increased dose through the cutoff date.

There were no reports of prohibited concomitant medications (phosphate, calcitriol, growth hormone). One patient received a single dose of prednisone for an allergic reaction to raw egg.

Efficacy Results - Primary Endpoint

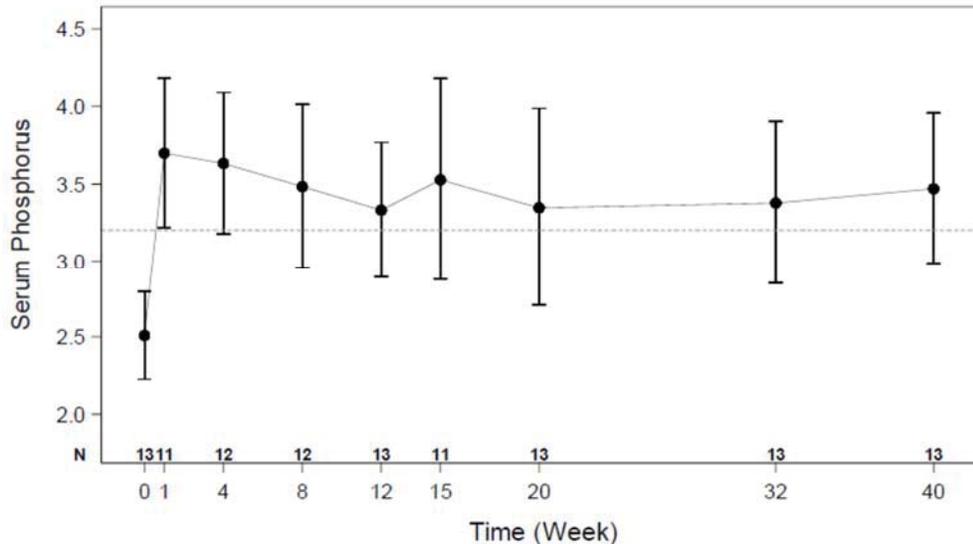
Reviewer Comments:

Preliminary study results at Week 24 were submitted in the original BLA submission, and primary analysis results at Week 40 were submitted during the BLA review process (submitted on 10/27/2018) and the data were submitted by Agency request on 11/27/2018).

Serum Phosphorus

Serum phosphorus increased promptly; mean level was >LLN at all time points (figure below). At week 40, mean (SD) serum phosphorus concentration was 3.47 (0.485) mg/dL; change from baseline to week 40 was +0.96 (0.439) mg/dL. All 13 subjects reached a serum phosphorus level within the normal range (3.2 to 6.1 mg/dL) at some point during the study. All 13 subjects had an increase in serum phosphorus from baseline to the average of post-baseline values that was at least 0.6 mg/dL. No patient had any level above the ULN (6.1 mg/dL) at any time.

Figure 42 Study CL205: Serum phosphorus, mean (SD) level (mg/dL) by visit (PK/PD Analysis Set)



Source: Fig. 14.2.3.1.1.99 submitted on 1/18/18
Dotted line \approx LLN for age (3.2 mg/dL)

Reviewer Comments:

Pharmacodynamic effects were more immediate in this study compared to study CL201 because of the difference in starting dose (0.8 mg/kg Q2W versus 0.1-0.3 mg/kg Q2W). At week 40, the two studies were nearly identical with respect to mean administered dose (0.89 versus 0.98 mg/kg Q2W) and mean change from baseline serum phosphorus (0.96 versus 0.92 mg/dL).

Data Quality and Integrity - Reviewers' Assessment

Review of the study conduct and submitted data did not raise any concerns about data quality or integrity.

Efficacy Results - Secondary and other relevant endpoints

RSS

As outlined in Table 63 below, there were significant improvements in rickets scores at week 40. LS-mean RSS total score declined from 2.92 to 1.19, a 59% reduction. Mean RSS wrist subscore declined from 1.27 to 0.50, a 61% reduction. Mean RSS knee subscore declined from 1.65 to 0.69, a 58% reduction. Mean RSS total score declined from baseline to week 40 in 11/13 patients, and did not change in the other 2.

RGI-C

Mean RGI-C global score at week 40 was +2.33; all 13 patients had scores ≥ 2 (“substantial healing” of rickets). Mean RGI-C wrist and knee subscores were similar (+2.26, +2.21 respectively). Improvements were consistent across the 5 skeletal sites for the specific radiographic abnormalities: metaphyseal lucency, fraying and concavity, and metaphysel/epiphyseal separation, with worsening not seen in any patient at any site.

RGI-C lower limb deformity scores were >0 for all 13 patients at week 40, with LS mean of +1.26. There were 3 (23%) patients with scores between 0 and <1 ; 8 (62%) patients with scores between 1 and <2 ; and 2 (15%) patients with scores between 2 and <3 . Improvements from baseline were observed in 69% and 54% of abnormal L and R femurs; 92% and 92% of abnormal L and R tibiae; and 25% and 15% of abnormal L and R fibulae; worsening was not noted in any of these bones in any patient.

Serum ALP

Serum ALP declined from baseline to week 40 in 13/13 patients, with a mean decline of 39%.

Table 63 Study CL205: Summary of Secondary Efficacy Endpoints

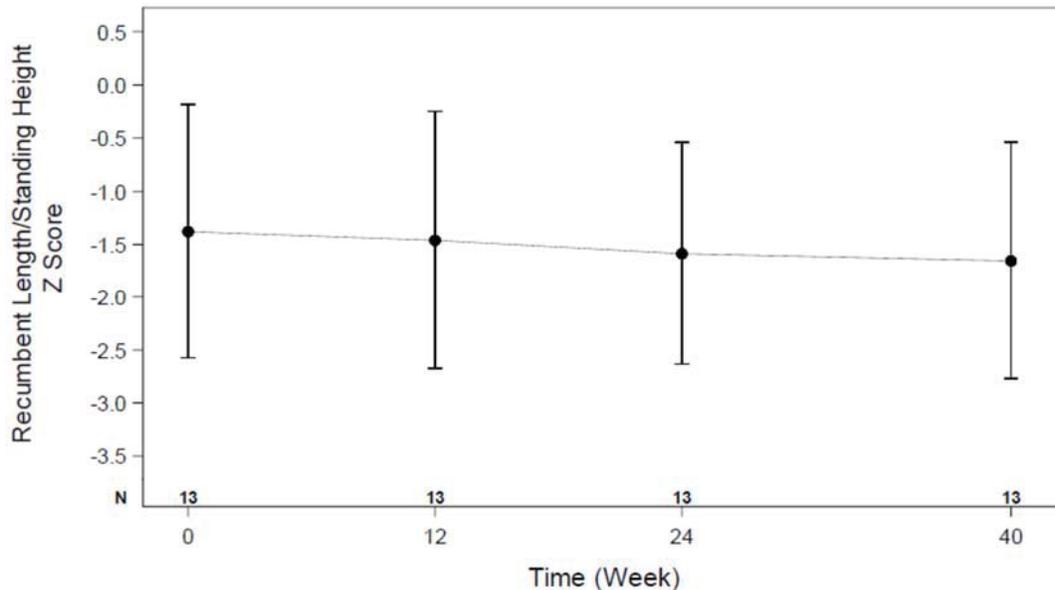
Endpoint	Baseline Mean (SD)	Week 40 Mean (SD)	Change to Week 40	
			LS mean (SE)	95% CI
RSS total score	2.92 (1.37)	1.19 (0.52)	-1.73 (0.13) ^a	(-2.03, -1.44)
RGI-C global score			2.33 (0.08) ^a	(2.16, 2.51)
RGI-C lower limb deformity score			1.26 (0.14) ^a	(0.94, 1.57)
Recumbent length/standing height Z-score	-1.38 (1.20)	-1.65 (1.12)	-0.20 (0.13) ^b	(-0.46, 0.06)
Recumbent length/standing height percentile	18.04 (25.26)	12.76 (18.94)	Mean (SD) -5.28 (20.168)	
Serum ALP (U/L)	548.5 (193.80)	335.4 (85.79)	-213.08 (13.53) ^c	(-239.59, -186.56)

a - LS mean (SE,) and 95% CI from the ANCOVA model, which included age and RSS total score at baseline as covariates.
 b - LS mean(SE) and 95% CI from the GEE model, which included visit and gender as factors, age and standing height Z score at baseline as covariates, with exchangeable covariance structure.
 c - LS mean(SE) and 95% CI from the GEE model, which included visit, and serum ALP at baseline as covariate, with exchangeable covariance structure.
 Source : CSR Table 14.2.1.1.1, Table 14.2.1.2.1, Table 14.2.1.2.2, Table 14.2.1.3.1, Table 14.2.3.3.1.1

Growth

Recumbent length or standing height mean (SD) increased from 89.2 (7.6) cm at baseline, to 93.4 (7.0) cm at week 40; individual changes ranged from +0.1 cm to +9.4 cm. However, age/gender normalized values showed trends of worsening over this interval: mean height percentile declined from 18.0% to 12.8%, and mean height Z-score declined from -1.38 to -1.65.

Figure 43 Study CL205: Growth: recumbent length or standing height Z-score, mean (SD) by visit (Efficacy Analysis Set)



Source: Fig. 14.2.1.3.1.99, submitted on 1/18/18

These measurements represent a mixture of standing height (7 patients), recumbent length (2 patients) and recumbent length changing to standing height during the study (4 patients). The week 40 CSR includes plots of individual height and height Z-score over time (Figs. 11.2.1 and 11.2.2) that appear to show that changes over time were generally consistent between the different methods of measurement (standing/recumbent).

Reviewer Comments:

The cause for this unfavorable trend in growth data, which is contrary to study CL201, is not apparent. As noted in the study report, the sample size is small and exposure time too short to reach firm conclusions. The report also notes that children with XLH typically begin to show a decline in growth velocity in this age range, attributed to beginning to walk and bear weight leading to bowing of legs and impaired growth plate function. To support this concept, height data on a total of 151 patients receiving conventional therapy (in study CL002, and historical data from study CL201 and CL205 patients before burosumab) were superimposed on CDC growth charts (Week 40 CSR Fig. 11.2.4). As stated in the report, these data are consistent with a gradual drop-off from growth norms in XLH patients occurring at approx. age 1-4 years.

Other PD efficacy endpoints

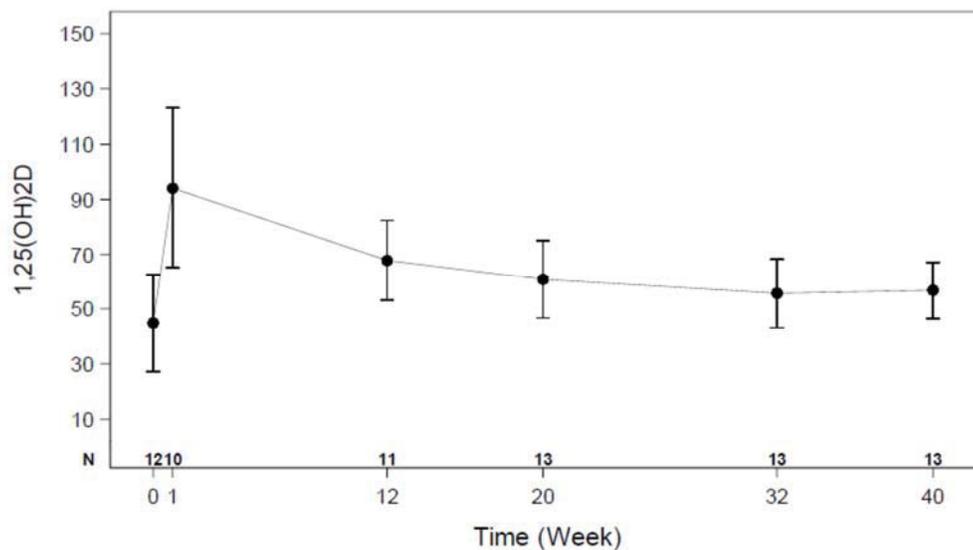
TmP/GFR

Because of the anticipated difficulty in obtaining 2-hr urine collections in these younger patients, TmP/GFR was not assessed in this study.

Serum 1,25(OH)₂ Vitamin D

Serum 1,25(OH)₂D mean level increased from 44.8 (17.6) pg/mL at baseline to 56.8 (10.3) pg/mL at week 40 (mean change: +43%). The increase was largest at 1 week after the first dose; subsequent measures were lower, but were collected at 2 weeks rather than 1 week following a dose (figure below).

Figure 44 Study CL205: Serum 1,25(OH)₂D, mean (SD) level (pg/mL) by visit (PK/PD Analysis Set)



Source: Fit. 14.2.3.2.1.99, submitted on 1/18/18

Durability of Response

No efficacy data beyond week 40 are yet available from this study.

8.1.4. Study UX023-CL303

Study title: 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)

Overview and Objective

The primary objective of this ongoing phase 3 study is to establish the effect of burosumab treatment, compared with placebo, on increasing serum phosphorus levels in adults with XLH.

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The key secondary objectives are to establish the effect of treatment, compared with placebo, on skeletal pain, stiffness and physical functioning. The study report submitted in the BLA, per agreement with the Division, evaluates primary efficacy and safety analyses using a cutoff of week 24.

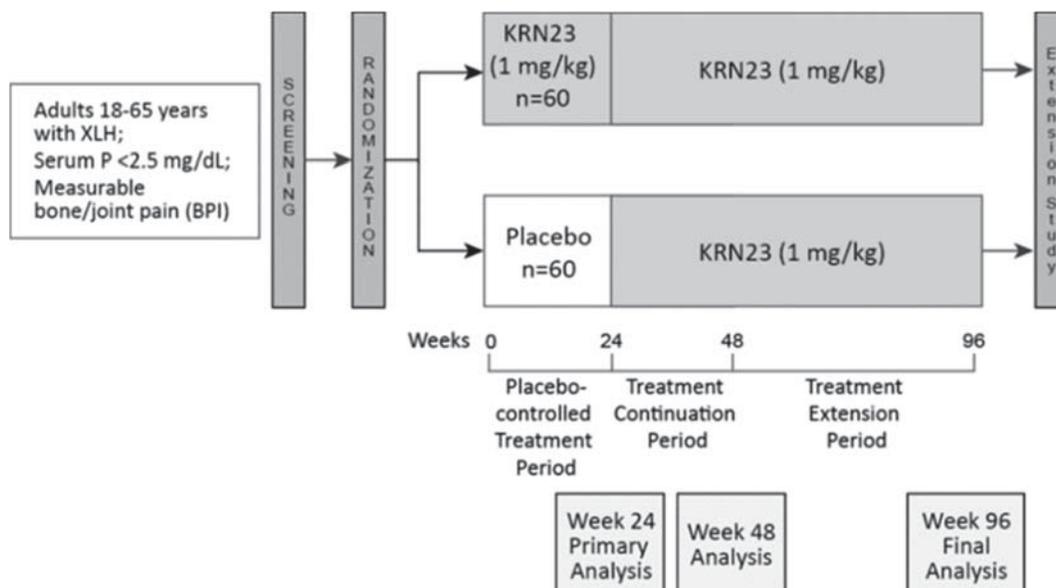
Study Design

This study, conducted at 25 centers in the US, Europe, Japan and S. Korea, was planned to enroll ~120 adults (age 18-65 years old) with XLH, hypophosphatemia and substantial bone or joint pain (BPI-Q3 pain score ≥ 4 on 0-10 scale, see below). Any patient receiving conventional therapy (active vitamin D and/or phosphate) was directed to discontinue at the first screening visit, so that off-treatment biochemical parameters could be assessed at the second screening and/or baseline visit, at least 2 weeks later.

Patients were randomized 1:1 to receive burosumab 1.0 mg/kg (rounded to the nearest 10 mg, to a maximum 90 mg) or placebo SC Q4W for the initial 24 weeks of treatment. Randomization was stratified by pain severity, based on mean BPI scores recorded in patient diaries during the week prior to the baseline visit. Per protocol, strata were defined by BPI-Q3 (worst pain) scores of 4 to ≤ 6 or >6 to 10. Because of a system error, BPI-Q5 (average pain) was actually used instead of BPI-Q3. Randomization was also stratified by region to assure balanced enrollment among Asian patients.

Following the primary analyses at week 24, all subjects receive open-label burosumab, 1.0 mg/kg Q4W. However, subjects and investigators remain blinded to the initial treatment assignment until week 48. In addition, subjects and investigators were blinded to key laboratory values expected to change substantially with burosumab, e.g. serum phosphorus.

Figure 45 Study CL303: Study Schema



Reviewer Comments:

Conventional therapy for XLH (phosphate/calcitriol) was not used in this study as an active control because efficacy and safety are not well established in adults, in addition to other issues with this treatment (lack of standardization of dose regimens, complexity of required monitoring and dosing adjustments, inability to blind subjects).

The burosumab dose used, 1.0 mg/kg Q4W, was based on phase 2 adult studies in which doses were titrated to achieve a serum phosphorus at the midpoint of the dosing interval (2 weeks post dose, which is approx. the peak) that was within the lower half of the normal range, i.e. 2.5-3.5 mg/dL. Most of the phase 2 patients stabilized in this range at the 1.0 mg/kg Q4W dose, the highest dose allowed in the studies, and none in studies INT-001/002 had any serum phosphorus level above normal range (>4.5 mg/dL).

Unlike the pediatric studies which allow dose increases if serum phosphorus remains below normal range, the 1.0 mg/kg Q4W dose is fixed in this adult study. The only exception is that in the event of high serum phosphorus (>5.0 mg/dL, or two consecutive levels >4.5 mg/dL, which is the ULN in adults), the dose is reduced by half.

Concomitant medications which are disallowed, including phosphate and calcitriol, are as listed below under enrollment exclusions. Vitamin D is permitted, and supplementation is to be provided if 25(OH)D levels fall below 20 ng/mL. Pain medications, including opioids are allowed.

Study population

The key inclusion criteria were as follows:

- Male or female, aged 18 – 65 years
- Diagnosis of XLH supported by classic clinical features of XLH (e.g. short stature or bowed legs) and at least one of the following:
 - Documented *PHEX* mutation in the patient or a directly related family member with appropriate X-linked inheritance
 - Serum iFGF23 level > 30 pg/mL (Kainos assay)
- Biochemical findings consistent with XLH (following overnight fast):
 - Serum phosphorus < 2.5 mg/dL
 - TmP/GFR < 2.5 mg/dL
- Skeletal pain attributed by the investigator to XLH/osteomalacia (and not solely due to other causes e.g. arthritis), with a score of ≥ 4 on the BPI-Q3 (Worst Pain) at screening visit 1.
- eGFR ≥ 60 mL/min (CKD-EPI) or eGFR 45-60 mL/min with confirmation that the renal insufficiency is not due to nephrocalcinosis
- If taking chronic pain medications (including opioids), must have been on a stable regimen, and ≤ 60 mg oral morphine equivalents/day
- Completed at least 4 of 7 days of the patient diaries before the baseline visit

The key exclusion criteria were:

- Active vitamin D analog (e.g. calcitriol) or oral phosphate within 14 days
- Aluminum hydroxide antacids, acetazolamides, or thiazides within 7 days
- Chronic use of systemic corticosteroids, defined as >10 days in the previous 2 months
- Evidence of hyperparathyroidism:
 - Corrected serum Ca ≥ 10.8 mg/dL
 - Serum iPTH ≥ 2.5 x ULN
 - Recent use of cinacalcet
- Use of bisphosphonates within 2 years
- Use of denosumab within 6 months
- Use of teriparatide within 2 months
- Planned or recommended orthopedic surgery within the first 24 weeks of the study
- History of traumatic fracture or orthopedic surgery within 6 months prior to screening

Reviewer Comments:

These criteria probably align well to recruit the largest component of the target adult XLH population, i.e. patients with substantial uncontrolled bone or joint pain. Because of the exclusion of patients with recent clinical fracture or planned orthopedic surgery, who are frequently treated with adjunctive conventional therapy with the goal of enhanced healing, the study was not specifically designed to evaluate this potential application of the drug.

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In a small proportion of patients with XLH by clinical criteria, PHEX testing is negative or inconclusive. In patients testing negative for PHEX mutations, other genetic testing was conducted for related conditions such as autosomal dominant hypophosphatemic rickets, etc.

Study Assessments

There were two screening visits, which included determination of eligibility, discontinuation of any phosphate or active vitamin D treatment and baseline assessments. The requirement for BPI-Q3 (worst pain in past 24 hrs) ≥ 4 on 0-10 scale was based on patient diary scores for the 7 days prior to the baseline visit.

During the double blind phase, subjects were seen (clinic or home visits) every 2 weeks. In the subsequent open label phase, visits (mostly home visits) are at 2- or 4-week intervals. Serum phosphorus and calcium are collected at most visits. Other efficacy measures (skeletal x-rays, PROs, 6MWT) are conducted every 12 weeks.

Study Endpoints

Primary efficacy endpoint: serum phosphorus

Hypophosphatemia is a defining feature of XLH and is believed to be the mechanism underlying all of the skeletal manifestations. In study CL303, the primary endpoint was the proportion of patients achieving mean serum phosphorus above LLN (2.5 mg/dL) at the midpoint of the 4-week dose interval, as averaged across dose cycles between baseline and week 24. That is, if a given patient's serum phosphorus levels at weeks 2, 6, 10, 14, 18 and 22 average to >2.5 mg/dL, the patient is considered a responder for this endpoint. Because serum phosphorus is subject to diurnal and postprandial changes, samples were collected after a minimum overnight fasting time of 8 hours; analyses were conducted by a central laboratory (b) (4).

Reviewer Comments:

The optimal extent and duration of increase in serum phosphorus levels required to heal osteomalacia in XLH and resolve symptoms is unclear. Based on phase 2 PK/PD data, the applicant powered study CL303 to demonstrate increased proportions of patients with normalized serum phosphorus both at midpoint of the dosing interval (2 weeks post dose) and trough (pre-dose). The latter is included among secondary PD endpoints (see below).

Secondary efficacy endpoints (patient-reported outcomes)

There were three "key" secondary endpoints based on PROs:

Brief Pain Inventory Question 3 (BPI-Q3-Worst Pain)

The BPI-Short Form is a self-reported, pain-specific PRO with a recall period of 24 hours, with questions related to pain severity and interference of pain with daily activities, and 0-10 NRS scale for each. Question 3, the outcome of interest, is "Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours", from 0 ("no pain") to 10

(“*pain as bad as you can imagine*”). For 7 consecutive days prior to baseline and prior to visits at weeks 12, 24, 36 and 48, patients recorded their responses in paper diaries, and the responses (up to 7) were averaged for each timepoint. Change from baseline at week 24 in Q3 score was compared between the treatment groups for this secondary endpoint. Patients also record all analgesic use in diaries during these 7-day periods.

Stiffness (WOMAC)

Stiffness and reduced range of motion are among the most common symptoms in adults with XLH, and may be due to osteoarthritis and/or progressive enthesopathy. The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) is a 24-item questionnaire developed for use in clinical trials in patients with osteoarthritis of the hip or knee, that evaluates domains of pain, stiffness and physical functioning. For the Stiffness domain, the WOMAC asks subjects to “*think about the stiffness (not pain) you felt in you ___ (study joint) caused by the arthritis during the last 48 hours. Stiffness is a sensation of decreased ease in moving your joint*”; and then to rate the severity of their stiffness in the morning and later in the day. Scores are 0-4 on Likert scales, with higher scores indicating worse stiffness; scores for the Stiffness domain of WOMAC are normalized and range from 0-100, representing the percent of maximal score.

Physical Function (WOMAC)

This WOMAC domain also has a 48-hour recall, and asks subjects to “*think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your ___ (study joint) during the last 48 hours*” and to rate their level of difficulty (0-4 Likert scale) with each of 17 different activities (e.g. going up or down stairs, bending, walking etc.) Scores for the Physical Function domain of WOMAC are normalized to a 0-100 scale as described above for the Stiffness domain.

In study CL303, based on FDA feedback, patients were instructed that when answering the WOMAC questionnaire, they should “**consider all lower extremity joints** including hips, knees, ankles and feet”, rather than a “study joint”, and “think about the pain/ stiffness/ difficulty with daily physical activities **caused by XLH** and not only arthritis” (bolded text as in instructions to site designated Clinical Evaluators).

Reviewer Comments:

Selection of specific PRO outcomes for adults with XLH was challenging due to the complex symptomatology and lack of published information on use of these instruments for XLH. Pain is a prominent symptom; the BPI-Q3 has been previously accepted by FDA in a variety of conditions, and COA staff agree with the applicant that the BPI-Q3 appears fit-for-purpose for the context of treatment of adults with XLH (see separate COA review). The WOMAC is used in a variety of rheumatic disorders and captures much of the musculoskeletal symptoms associated with XLH, however the references to “arthritis” and “study joint” are problematic, and the applicant was advised during protocol development that the WOMAC may not be suitable. Upon review of all information submitted to the BLA, the COA staff believes that patients cannot

reliably differentiate the symptoms of XLH and arthritis, and may have been confused by the instructions, and that the WOMAC is not fit-for-purpose for this development program.

Other endpoints

PD endpoints

- Serum phosphorus: In addition to the primary endpoint (mid-dosing-cycle phosphorus), serum phosphorus was evaluated at the end of dosing cycles (4 weeks post dose)
- Serum 1,25(OH)D, urinary phosphate, Tmp/GFR, TRP: These PD markers provide insight into the mechanism of action of burosumab.

Other PRO endpoints

- Pain severity: In addition to the primary endpoint, BPI Question 3 (worst pain in the past 24 hours), subjects rate other aspects of pain severity (least pain and average pain in the past 24 hours, and pain “right now”, i.e. BPI Questions 4, 5 and 6). These 4 responses (over 7 days prior to visits at baseline, weeks 12 and 24) are combined into the BPI Pain Severity score.
- Impact of pain on functioning: Questions 9a-9g of the BPI asks subjects to “describe how, during the past 24 hours, pain has interfered with your [general activity, mood, walking ability, normal work (includes both work outside the home and housework), relations with other people, sleep, enjoyment of life]”. Each of these 7 scores (on 0-10 NRS scale) are combined into the BPI Pain Interference score.
- Fatigue: the Brief Fatigue Inventory (BFI), like the BPI, asks subjects to score symptoms on 1-10 NRS scales with a recall period of 24 hours. BFI Question 3 asks patients to score their worst level of fatigue, and the BFI Global Fatigue score combines all 9 items in the BFI measuring fatigue severity (now, usual, and worst) and the extent to which fatigue has interfered with the patient’s general activity, mood, walking ability, normal work (includes both work outside the home and daily chores), relations with other people, and enjoyment of life. The BFI has been used in arthritis and other musculoskeletal conditions.

Bone turnover markers

Serum P1NP, CTX and BALP were evaluated and demonstrated increases from baseline in the phase 2 studies, which the sponsor believes is an indicator of improvement (replacement of hypomineralized bone). These markers were evaluated in this phase 3 study with samples collected in a serial manner after an overnight fast.

Exploratory endpoints

Healing of fractures/pseudofractures

Patients with osteomalacia are at risk of developing pseudofractures (Looser zones), atraumatic fractures and/or impaired fracture healing, in part because excess osteoid impairs the ability of osteoclasts to initiate remodeling for repair of microdamage. In study CL303, a baseline skeletal survey (bilateral upper and lower extremities, chest, lateral spine) was conducted to identify

pre-existing pseudofractures (defined as lucency extending across one cortex of the involved bone) and fractures (involving both cortices). Active (non-healed) fractures/pseudofractures were those with a visible fracture line. Non-active (healed) fracture/pseudofractures were those with cortical thickening/contour deformity with no evidence of active fracture line, with fracture callus across the entire bone and pseudofracture callus involving 1 cortex.

Active lesions were followed up with additional radiographs at weeks 12 and 24, but the full skeletal survey was not repeated. Two central readers, with a third for adjudication as needed, who were blinded to treatment assignment, compared baseline and follow-up images and graded each fracture or pseudofracture for changes according to the following scale:

- Healed: focal cortical thickening/contour deformity with no evidence of fracture line
- Partially healed: fracture line is partially visible and partially obscured by callus formation
- Unchanged: fracture line remains visible without any evidence of healing when compared to the prior exam
- Worse, e.g. widening of fracture line, fracture to completion/across entire bone, displacement of fracture

The overall number of, and also the number of patients with, active pseudofractures and/or fractures at baseline that resulted in each of these outcomes through week 24 were designated as exploratory endpoints in this study.

Enthesopathy is a common feature of XLH in adults. Calcification of calcaneal tendons by lateral foot xrays was captured in the baseline skeletal survey, and follow-up lateral foot xrays at weeks 24, 48 and 96 were added to the protocol in amendment 1. The length of spurs at both the superior and inferior calcaneus were added for this endpoint.

6 Minute Walk Test was conducted to evaluate ambulatory function at baseline and weeks 12, 24, 36, 48 and 72.

Statistical Analysis Plan

Randomization

Eligible subjects were randomized in a 1:1 ratio to placebo or burosumab group. Randomization was stratified by mean BPI-Q5 diary scores for the 7 days prior to the Baseline visit (>6.0, or ≤6.0) and by region (North America/EU, Japan, and South Korea).

Reviewer Comments:

The study was planned to randomize patients stratified by BPI-Q3 (worst pain). However, the IWRS erroneously used BPI-Q5 (average pain) as the stratification factor instead. The applicant identified this error as study enrollment and dosing were already ongoing and determined that the study should continue with subsequent enrollment under the implemented stratification factor BPI-Q5 instead of changing and correcting the BPI stratification factor back to the

protocol specified BPI-Q3 midway into the study. All enrolled subjects were affected by this IWRS error. The applicant included the IWRS error to the list of protocol violations. Although all subjects were affected by this protocol violation, they were included in the primary efficacy analysis.

The applicant conducted a sensitivity analysis using the protocol specified randomization stratification factor based on BPI Worst Pain (>6.0 or ≤6.0) as a substitute for the actual stratification factor based on BPI Average Pain in the primary analysis to assess the impact of the stratification misclassification on randomization.

Sample size

Sample size was calculated based on assuming that the proportion of subjects who achieve mean serum phosphorus levels above the lower limit of normal at the mid-point of the dose interval (2 weeks post-dose) from Baseline to Week 24 (i.e., mean of Weeks 2, 6, 10, 14, 18, and 22) in the burosumab and placebo treatment groups is 60% and 10%, respectively. A sample size of 60 per group (total sample size of 120) would provide greater than 95% power to detect a 50% difference in the proportion of subjects who achieve mean serum phosphorus levels above the lower limit of normal at the mid-point of the dose interval from Baseline to Week 24 between the burosumab and placebo treatment groups at a 2-sided level of significance of 0.05.

Interim analysis

The study report submitted in this BLA summarized the primary efficacy analysis after all subjects completed the Week 24 assessments or discontinued during the placebo-controlled treatment period. The subject's treatment assignment was unblinded to the applicant for the Week 24 primary efficacy analysis.

A Week 48 analysis will be conducted after all subjects have completed the Week 48 assessments or discontinued from the study during the Treatment Continuation Period to assess longer-term treatment efficacy and safety. The final analysis will be performed after all subject have completed the Week 96 assessments or discontinued from the study and the study database has been locked.

Analysis Populations

The following analysis populations are defined in the statistical analysis plan for the Week 24 analysis:

- Primary analysis set: All randomized subjects who received at least one dose of investigational product during the Placebo-Controlled Treatment Period. The primary analysis set was used for the analysis of efficacy endpoints at each specific analysis milestone (eg, week 24, 48 or 96). Subjects were analyzed per the randomized treatment group, regardless of the actual treatment received.

- Safety Analysis Set: All randomized subjects who received at least one dose of investigational product. This analysis set was used for the analyses of all safety endpoints. Subjects were analyzed based on the actual treatment received. The safety analysis set was used for the analysis of the safety endpoints at each specific analysis milestone (eg, Weeks 24, 48 or 96).

Handling of Missing and Incomplete Data

For the primary efficacy endpoint, if no serum data was available to evaluate, the subject was considered as not achieving a serum phosphorus level above the LLN.

For computing the domain scores at each visit for each subject, the WOMAC missing data algorithm is as follows:

1. If two or more Pain items, both stiffness items, or four or more physical functioning items were missing, then the corresponding scale score was set to missing.
2. Otherwise, any missing item was replaced with the mean of the other items in its scale, and scales were then calculated normally.

For the BPI and BFI endpoints at each visit, the following imputation rules were applied:

1. If the score for the endpoint was missing at the scheduled visit, the endpoint was set to missing at this visit.
2. Otherwise, for the endpoints of BPI pain severity dimensions, BPI severity score and BFI fatigue severity items which were derived based on the diary score, if there were more than 3 of 7 daily diary scores missing for the endpoint prior to the study scheduled visit, the score recorded at the scheduled visit was used for this visit.
3. Otherwise, the average of the non-missing diary scores and the score recorded at the visit was used for this visit.

Multiplicity Control

In order to control the family-wise error rate (FWER) at the 0.05 level, the following multiple testing procedure was applied to the primary endpoint and three secondary PRO endpoints (BPI Worst Pain, WOMAC stiffness and WOMAC physical function) for the week 24 primary analysis:

- Step 1: Test the primary endpoint of the proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal at the mid-point of the dose interval. If KRN23 treatment group was superior to the placebo group (p -value < 0.05 using a two-sided test), then go to Step 2, otherwise stop testing.
- Step 2: Test the three secondary PRO endpoints (change from baseline to week 24 in BPI Worst Pain, WOMAC stiffness, and WOMAC physical function) between treatment groups as a group at 0.05 level. Hochberg adjustment was applied for multiple testing of these three endpoints.

Efficacy Analysis Methods

All efficacy analyses were done using the primary analysis set unless otherwise stated. The observed measures and the change from baseline for each efficacy endpoint were summarized using descriptive summary statistics. A GEE model was used to analyze the change from baseline over time for some efficacy endpoints. The GEE model included treatment, randomization stratification factor based on BPI-Q5 (average pain: > 6.0 or ≤ 6.0), region, visit and interaction of treatment-by-visit as fixed factors, and baseline value as covariate. A compound symmetry covariance matrix was used in the GEE model to specify constant variance for the assessments and constant covariance between the assessments over time. The p-value for testing the statistical significance of the change from baseline to week 24 between the two treatment groups, the LS mean estimate of the change from baseline for each treatment group, the LS mean estimate of the difference between treatment groups, and 95% CIs were reported.

The following efficacy endpoints were analyzed using the approaches outlined in the statistical analysis plan.

Serum phosphorus

The primary endpoint was analyzed using the Cochran-Mantel-Haenszel (CMH) test to compare the proportion of subjects in the burosumab group and the placebo group who achieved a serum phosphorus level above the LLN (2.5 mg/dL [0.81 mmol/L]) at 2 weeks post-dose (between Baseline and Week 24, on average), adjusting for the actual stratification factors used for randomization: BPI Average Pain (> 6.0 or ≤ 6.0) and region.

In the case where no serum phosphorus data were available for 2 weeks post-dose between Baseline and Week 24, that subject was treated as a non-responder, defined as not achieving a serum phosphorus level above the LLN. The primary endpoint was tested at the 2-sided alpha level of 0.05.

BPI worst pain, WOMAC stiffness and WOMAC physical function

Change from baseline over time for each endpoint was analyzed using a GEE model as described above. For analysis of change from baseline in BPI worst pain, the stratification factor based on BPI average pain was not included in the GEE model because baseline BPI Worst Pain is highly correlated with the randomization stratification factor based on BPI Average Pain between Baseline and Week 24.

Secondary PD endpoints

Descriptive summaries of the following secondary PD endpoints were provided by treatment groups for the Week 24 analysis:

- Proportion of subjects achieving mean serum phosphorus levels above the LLN (2.5 mg/dL [0.81 mmol/L]) at the end of the dosing cycle (4 weeks after dosing), averaged across dose cycles between baseline and Week 24.
- Mean change from baseline and percent change from baseline in serum phosphorus at each mid-point of dosing cycle, averaged across dose cycles between baseline and Week 24.
- Mean change from baseline and percent change from baseline in serum phosphorus at each end of dosing cycle, averaged across dose cycles between baseline and Week 24.
- Time-adjusted area under the curve (AUC) of serum phosphorus between baseline and Week 24.

Treatment group comparisons at week 24 for the following key PD efficacy endpoints were tested using a GEE model:

- Change and percent change from baseline to post-baseline visits in serum phosphorus, serum 1,25(OH)₂D, urinary phosphorus, ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR), and tubular reabsorption of phosphate (TRP)

Healing of pseudofractures and fractures

The number of active (non-healed) pseudofractures and/or fractures as defined by skeletal survey at baseline and the number and percentage of the baseline active pseudofractures/fractures which healed, partially healed, were unchanged or worsened at post-baseline visits was summarized by treatment groups. New active pseudofractures and/or fractures identified at post-baseline visits were also summarized by treatment groups.

The number of subjects with baseline active pseudofractures and/or fractures and the number of these subjects who had changes from baseline to healed, partially healed, unchanged and worsened at post-baseline visits was summarized by treatment group. The number of subjects with new active pseudofractures and/or fractures at post-baseline visits was also summarized by treatment groups.

Protocol Amendments

The original protocol was dated 6/5/2015. Amendments 1 and 2 (7/21/2016 and 9/8/2016) made various changes, including addition of a 48-week extension to the initial 48-week design.

Amendment 3 (3/31/2017), reflecting changes in the SAP, modified the secondary objectives and endpoints based on the applicant's assessment that physical functioning and stiffness were of equal importance to pain as clinical outcomes. Thus, the WOMAC Stiffness and WOMAC Physical Function scores were elevated from "other" to "key secondary" endpoints to complement the BPI-Q3 Worst Pain score, and the secondary objective was now "to establish

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the effect of KRN23 treatment compared with placebo on skeletal pain, stiffness, and physical functioning”.

Study Results

Compliance with Good Clinical Practices

The applicant attests that study CL303 has been conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP).

Financial Disclosure

Study CL303 is among the covered clinical studies, as defined by 21 CFR 54.2(e), which provide the primary evidence establishing the effectiveness and safety of burosumab (see Appendix 15.2). The applicant has adequately disclosed financial interests/arrangements with the clinical investigators as recommended in FDA guidance, and no concerns are raised about the integrity of the data.

Patient Disposition

There were 166 individuals screened for study CL303 and 134 were enrolled. The most common reasons for screen failure were BPI worst pain score <4 (10 patients) and serum iPTH \geq 2.5 (5 patients). The following table lists the highest-enrolling sites (\geq 5 patients), which includes 7 of the 8 US sites. Overall, 69/134 (51%) of randomized patients were at US sites; 35% were European and 13% were Asian.

Table 64 Study CL303: Enrollment by site*/country

Site #	Investigator	Site Location	Country	# patients screened	# patients enrolled
138	Carpenter	Yale Univ.	USA	20	18
139	Portale	UCSF	USA	12	9
142	Pitukcheewanont	Childrens Hosp. LA	USA	10	6
156	Imel	Indiana Univ.	USA	16	12
162	Ruppe	Houston Methodist Hosp.	USA	11	10
163	Weber	Duke	USA	7	6
175	Jan De Beur	Johns Hopkins	USA	6	5
185	Roux	CHU Paris Centre	France	15	15
186	Kamenicky	CHU de Bicetre	France	12	12
199	Cheong	Seoul Nat. Univ. Hosp.	S. Korea	5	5
Total USA				87	69
Total France				33	30
Total UK				17	11
Total Japan				12	11
Total S. Korea				8	7
Total Ireland				6	3
Total Italy				3	3
Total all sites				166	134
*highest-enrolling sites (≥5 enrollees) are listed Source: CSR Table 16.1.4.1.1					

The 134 enrolled patients were randomized 1:1 to burosumab (N=68) or placebo (N=66). One patient (burosumab) discontinued because “withdrew consent” at about 5 months, and the remaining 133 patients completed the initial 48 weeks. After the week 48 visit, 7 patients chose not to participate in the Treatment Extension period, and 2 patients became pregnant and withdrew from the study. After the data cutoff for the 120-day safety update, one patient died in an automobile accident (see section 10.4.1).

The Primary Analysis Set and Safety Analysis Set include all 134 randomized patients. Per protocol, randomization strata were defined by BPI-Q3 (worst pain) scores of 4 to ≤6 or >6 to 10; but because of a system error, BPI-Q5 (average pain) was actually used instead of BPI-Q3, with the same score criteria of 4 to ≤6 and >6 to 10.

Protocol Violations/Deviations

Major protocol deviations were reported on 45% of patients. Most instances involved procedures not done or fasting status not documented for blood draws. One patient (# (b) (6)) was enrolled despite a baseline serum phosphorus of 3.0 mg/dL; no other significant enrollment criteria violations were identified.

It should be noted that all subjects were affected at randomization by the IWRS using the wrong stratification factor based on BPI-Q5 (average pain) instead of using the specified factor based on BPI-Q3 (worst pain). Both factors were based on pain. The sponsor conducted a sensitivity analysis using BPI-Q3 and the results were not different from those using BPI-Q5.

Demographic Characteristics

The average age of CL303 participants was 40 years. About 2/3 were female, consistent with the X-dominant inheritance of XLH. Most patients were white (81%) or Asian (16%), and most were non-Hispanic (91%). The randomized treatment groups were generally similar.

Table 65 Study CL303: Demographic characteristics (PAS)

	Placebo (N=66)	KRN23 (N=68)	Total (N=134)
Sex – n (%)			
Male	23 (35)	24 (35)	47 (35)
Female	43 (65)	44 (65)	87 (65)
Age			
Mean years (SD)	38.7 (12.8)	41.3 (11.6)	40.0 (12.2)
Min, max (years)	18.5, 65.5	20.0, 63.4	18.5, 65.5
Race – n (%)			
White	53 (80)	55 (81)	108 (81)
Asian	9 (14)	12 (18)	21 (16)
Black or African American	3 (5)	0	3 (2)
Other	1 (1.5)	1 (1.5)	2 (1.5)
Ethnicity – n (%)			
Hispanic or Latino	5 (8)	7 (10)	12 (9)
Not Hispanic or Latino	61 (92)	61 (90)	122 (91)
BMI, mean	30.6	30.0	30.3
Source: CSR Table 14.1.2.1			

Other Baseline Characteristics

Participants reported that their first XLH symptoms occurred at an average age of 3 years and that XLH was diagnosed at an average age of 9. Most patients (81%) had received conventional therapy before the age of 18, for an average of ~12 years. Most (83%) had also received therapy after the age of 18, for an average of ~9 years, and 69% of patients had used phosphate and/or active vitamin D within 2 years of study baseline.

Most patients (69%) reported prior orthopedic surgery, including 57% with prior osteotomy to correct a deformity. Patients also reported histories of a fracture (43%), most commonly of the femur (27%); genu varum/bowing (75%); genu valgum/knock knees (17%); intoeing (24%); widened wrists (19%); osteoarthritis (63%), most commonly in the knee (46%) or hip (40%); bone spurs/osteophytes (40%); enthesopathy (37%); and spinal stenosis (19%). In addition, 86%

reported dental disorders including 63% with tooth abscess. Nephrocalcinosis and/or nephrolithiasis history was reported by 23% of patients.

Baseline data related to XLH disease activity (laboratory, radiographic and patient-reported) are listed in Table 66 below. Mean serum phosphorus (1.98 mg/dL) and mean TmP/GFR (1.64 mg/dL) were low and mean 1,25(OH)₂D (33.0 pg/mL) was normal, which are typical findings for adults with untreated XLH (there was a 2-week washout for oral phosphate or vitamin D analogs prior to these baseline values). Large majorities of patients had radiographic bowing (both upper and lower extremities) and enthesopathy. Skeletal surveys showed active fractures (non-healed) in 12% of patients and active pseudofractures in 47%, mostly in the weight-bearing bones of the lower extremities. Average BPI-Q3 (worst pain) score was 6.68 (on NRS 0-10 scale) and average BPI-Q5 (average pain) score was 5.10.

The most common pain locations at baseline were lower extremity (96%, mostly hip and knee); back/spine (67%) and upper extremity (54%, mostly shoulder). NSAID and/or acetaminophen use was reported by 67% of patients and opioid use by 22%.

Table 66 Study CL303: XLH related baseline characteristics (PAS)

	Placebo (N=66)	KRN23 (N=68)	Total (N=134)
Serum phosphorus (mg/dL), n*	66	68	134
Mean (SD)	1.92 (0.32)	2.03 (0.30)	1.98 (0.31)
Min, max	1.3, 2.6	1.3, 3.0	1.3, 3.0
TmP/GFR (mg/dL), n	64	66	130
Mean (SD)	1.60 (0.37)	1.68 (0.40)	1.64 (0.39)
Min, max	0.71, 2.62	0.95, 3.41	0.71, 3.41
Serum 1,25(OH) ₂ D (pg/mL), n*	64	66	130
Mean (SD)	33.5 (15.6)	32.4 (13.0)	33.0 (14.3)
Min, max	4, 80	4, 76	4, 80
Radiographic bowing, overall, n (%)	62 (94)	64 (94)	126 (94)
Upper extremity bowing, n (%)	59 (89)	58 (85)	117 (87)
Lower extremity bowing, n (%)	55 (83)	60 (88)	115 (86)
Enthesopathy (any location), n (%)	65 (99)	68 (100)	133 (99)
Active fractures (any location), n (%)	8 (12)	8 (12)	16 (12)
Non-active fractures (any location), n (%)	37 (56)	42 (62)	79 (59)
Active pseudofractures (any location), n (%)	34 (52)	29 (43)	63 (47)
Non-active pseudofractures (any location), n (%)	22 (33)	24 (35)	46 (34)
BPI Worst Pain (Q3), mean (SD)	6.54 (1.43)	6.81 (1.31)	6.68 (1.37)
≤ 6.0	23 (35)	15 (22)	38 (28)
>6.0	43 (65)	53 (78)	96 (72)
BPI Average Pain (Q5), mean (SD)	5.05 (1.48)	5.14 (1.56)	5.10 (1.52)
*Reference ranges: serum phosphorus=2.5-4.5 mg/dL; serum 1,25(OH) ₂ D=18-72 pg/mL Sources: CSR Table 14.1.2.1.99.1, Table 14.2.1.7.2			

Genetic testing identified *PHEX* mutations in 94% of patients, including mutations historically shown to be pathogenic (70%), likely pathogenic (11%), and variants of uncertain significance (13%). In the remaining 7 patients with no *PHEX* mutation identified, the protocol inclusion criterion for support of the XLH diagnosis was met by serum FGF23 levels >30 pg/mL; four of these also had affected family members. The applicant continues to test these patients to identify other genes associated with phenotypes overlapping with XLH.

Subgroup analyses by the applicant showed that females had somewhat higher pain levels at baseline (67% of BPI-Q3 >6.0 group, vs. 55% of BPI-Q3 ≤6.0 group), and Asian patients the reverse (13% vs. 24%). Patients in the higher-pain group were somewhat less likely to have received conventional therapy in adulthood, and had shorter duration of treatment.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were no patients reported to use concomitant oral phosphate, and only one patient (# (b) (6)) who briefly used an active vitamin D analog (alfacalcidol). There was minimal use of other disallowed concomitant medications: patient # (b) (6) took HCTZ for 2 months, and patient # (b) (6) underwent steroid injection in both knees due to increased pain.

Efficacy Results - Primary Endpoint, Serum phosphorus

A total of 94.1% of subjects in the KRN23 group achieved a mean serum phosphorus concentration above the LLN (2.5 mg/dL) across the midpoints of the dose intervals through Week 24, compared with only 7.6% of subjects in the placebo group ($p < 0.0001$).

Table 67 Study CL303: Proportion of subjects achieved Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24 – Primary Analysis (PAS)

Primary Efficacy Endpoint	Placebo (N = 66)	KRN23 (N = 68)
Achieved Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24		
n (%)	5 (7.6)	64 (94.1)
95% CI	(3.3, 16.5)	(85.8, 97.7)
p-value		< 0.0001
PAS: primary analysis set. p-value is from Cochran-Mantel-Haenszel (CMH) adjusting for the stratification factors. Source: CSR Table 14.2.3.1.1		

Subgroup analysis for primary efficacy endpoint

Large increase in mid-dose interval serum phosphorus was consistent across subgroups of age, baseline BPI pain scores, geographic region, sex and race.

Reviewer Comments:

The subgroup analysis by age was conducted by FDA statistical reviewer.

Table 68 Study CL303: Proportion of Subjects Who Achieved a Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24 by Subgroups – (PAS)

Achieved Mean Serum Phosphorus > LLN	Statistics	Placebo (N = 66)	KRN23 (N = 68)
Age			
<=50 years old	n/N1 (%) 95% CI	3/54(5.6) (1.2, 15.4)	49/52 (94.2) (84.6, 98.8)
>50 years old	n/N1 (%) 95% CI	2/12 (16.7) (2.1, 48.4)	15/16 (93.8) (69.8, 99.8)
BPI Worst Pain			
<=6.0	n/N1 (%) 95% CI	3/23 (13.0) (4.5, 32.1)	15/15 (100.0) (79.6, 100.0)
>6.0	n/N1 (%) 95% CI	2/43 (4.7) (1.3, 15.5)	49/53 (92.5) (82.1, 97.0)
BPI Average Pain			
<=6.0	n/N1 (%) 95% CI	4/49 (8.2) (3.2, 19.2)	45/48 (93.8) (83.2, 97.9)
>6.0	n/N1 (%) 95% CI	1/17 (5.9) (1.0, 27.0)	19/20 (95.0) (76.4, 99.1)
Geographical Regions			
North America/EU	n/N1 (%) 95% CI	5/58 (8.6) (3.7, 18.6)	56/58 (96.6) (88.3, 99.0)
Japan	n/N1 (%) 95% CI	0/5 (0.0) (0.0, 43.4)	6/6 (100.0) (61.0, 100.0)
South Korea	n/N1 (%) 95% CI	0/3 (0.0, 56.1)	2/4 (50.0) (15.0, 85.0)
Sex			
Male	n/N1 (%) 95% CI	1/23 (4.3) (0.8, 21.0)	22/24 (91.7) (74.2, 97.7)
Female	n/N1 (%) 95% CI	4/43 (9.3) (3.7, 21.6)	42/44 (95.5) (84.9, 98.7)
Race			
White	n/N1 (%) 95% CI	5/53 (9.4) (4.1, 20.3)	53/55 (96.4) (87.7, 99.0)
Non-White	n/N1 (%) 95% CI	0/13 (0.0) (0, 22.8)	11/13 (84.6) (57.8, 95.7)

N1 is the number of subjects in the subgroup; n is the number of subjects who Achieved Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24

Source: Reviewer's Analysis. CSR Table 14.2.3.1.4, Table 14.2.3.1.3, Table 14.2.3.1.5, Table 14.2.3.1.12, Table 14.2.3.1.13

Secondary Analysis of Serum Phosphorus

Other parameters of serum phosphorus also showed large increases with burosumab relative to placebo, including the mean changes in serum phosphorus across the midpoints and ends of the 4-week dosing cycles to week 24. Most burosumab recipients (68%) achieved normal mean phosphorus levels across troughs as well as peaks.

Table 69 Study CL303: Serum Phosphorus Secondary Analyses – (PAS)

Parameter Statistics	Placebo (N = 66)	KRN23 (N = 68)
Serum phosphorus, mg/dL Baseline mean (SD) Week 24 mean (SD)	1.92 (0.32) 2.07 (0.34)	2.03 (0.30) 2.53 (0.45)
Serum phosphorus across the midpoints of the dose cycles to Week 24, mg/dL Mean (SD) Mean change (SD) from baseline Mean percentage change (SD) from baseline, %	2.08 (0.30) 0.16 (0.27) 9.87 (15.29)	3.24 (0.53) 1.21 (0.51) 61.43 (28.84)
Achieved mean serum phosphorus > LLN across the ends of the dose intervals through Week 24 n (%) 95% CI ^a	4 (6.1) (2.4, 14.6)	46 (67.6) (55.8, 77.6)
Serum phosphorus across the ends of the dose cycles to Week 24 Mean (SD), mg/dL Mean change (SD) from baseline, mg/dL Mean percentage change (SD) from baseline, %	2.05 (0.30) 0.13 (0.26) 7.83 (14.76)	2.72 (0.45) 0.69 (0.39) 35.21 (20.70)
Time-adjusted AUC of serum phosphorus between baseline and Week 24 Mean (SD), mg/dL	2.08 (0.29)	3.08 (0.48)
Serum phosphorus at Week 24 Mean change (SD), mg/dL LS mean change (SE) from baseline, mg/dL Mean percentage change (SD) from baseline, % LS mean percentage change (SE) from baseline, %	0.15 (0.35) 0.03 (0.07) 9.20 (19.31) 2.08 (3.55)	0.49 (0.39) 0.42 (0.08) 25.38 (20.18) 22.36 (3.97)
<p>The conversion factor from conventional units (mg/dL) to SI units (mmol/L) is 0.323.</p> <p>a The 95% CIs for the percentage of subjects who achieve mean serum phosphorus levels above the LLN are calculated using Wilson score method.</p> <p>b LS means are from the generalized estimation equation (GEE) model, which includes the change from baseline or percent change from baseline for serum phosphorus as the dependent variable; region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors; and baseline of serum phosphorus as a covariate, with symmetry covariance structure.</p> <p>Source: CSR Table 14.2.3.1.6, Table 14.2.3.1.7, Table 14.2.3.1.8, Table 14.2.3.1.9, Table 14.2.3.1.10</p>		

Data Quality and Integrity - Reviewers' Assessment

The applicant identified a system error by which radiograph assessments of fracture and pseudofracture healing did not consistently use the baseline image as intended. Thus, the central readers were re-trained, and radiographs were re-interpreted using the correct

comparator and preserving the blinding to treatment assignment; the amended data yielded no change in the conclusions. No other potential data integrity issues were identified during review of this application.

Efficacy Results - Secondary and other relevant endpoints

Secondary PRO Endpoints

Because the primary endpoint of serum phosphorus was met, the secondary endpoints of changes from baseline to week 24 in BPI Worst Pain, WOMAC Stiffness, and WOMAC Physical Function scores were tested between the treatment groups. As outlined in the table below, only one of these endpoints (WOMAC Stiffness) achieved statistical significance under the prespecified Hochberg multiplicity adjustment, although the BPI Worst Pain and WOMAC Physical Functioning endpoints also showed favorable trends at week 24 for burosumab. For all 3 of these endpoints, burosumab-placebo differences at week 12 were smaller than at week 24.

Table 70 Study CL303: BPI Worst Pain, Physical Functioning, Stiffness by WOMAC and Change from baseline at Week 24 – Secondary Analysis (PAS)

Secondary Endpoint		Statistics	Placebo (N = 66)	KRN23 (N = 68)
Worst Pain, by BPI	Baseline	Mean (SD)	6.54 (1.43)	6.81 (1.31)
	Change from Baseline	LS Mean (SE)	-0.32 (0.22)	-0.79 (0.21)
		Difference vs. placebo		-0.46 (0.28)
		95% CI		(-1.00, 0.08)
		P-value		0.0919 ^a
Physical Functioning, by WOMAC	Baseline	Mean (SD)	43.89 (19.94)	50.79 (19.66)
	Change from Baseline	LS Mean (SE)	1.79 (2.72)	-3.11 (2.55)
		Difference vs. placebo		-4.90 (2.50)
		95% CI		(-9.76, -0.05)
		P-value		0.0478 ^b
Stiffness, by WOMAC	Baseline	Mean (SD)	61.74 (21.25)	64.71 (20.25)
	Change from Baseline	LS Mean (SE)	0.25 (3.13)	-7.87 (3.04)
		Difference vs. placebo		-8.12 (3.24)
		95% CI		(-14.46, -1.77)
		P-value		0.0122^c
LS means and p-values are from the generalized estimation equation (GEE) model a The significance level is 0.05, the test is not statistically significant b The significance level is 0.025, the test is not statistically significant c The significance level is 0.0167, the test is statistically significant Source: CSR Table 14.2.1.1.1, Table 14.2.1.2.1.1, Table 14.2.1.2.2.1				

Prespecified responder analyses were based on BPI-Q3 decreases of $\geq 15\%$ (or 2-point decrease) or $\geq 30\%$; and for the WOMAC, decreases of ≥ 9.3 for Physical Function or ≥ 10 for Stiffness (which are the estimates of minimally important change [MIC] as listed in the WOMAC Users Manual). For each of these parameters there were numerically more responders in the

burosumab group, but none of the treatment group differences approached statistical significance.

Prespecified subgroup analyses for these secondary endpoints were conducted by BPI Worst Pain (≤ 6.0 , >6.0), BPI Average Pain (≤ 6.0 , >6.0), region (N. America/EU, Japan, S. Korea), sex and race. Males tended to show greater numerical improvement in each of the 3 endpoints (pain, stiffness, physical function) compared to females, and some endpoints favored placebo among Japanese, S. Korean or non-white patients, but were based on very small numbers. Otherwise, there were fairly consistent trends favorable to burosumab with these endpoints/ subgroups.

Other PRO endpoints

Additional prespecified endpoints based on the BPI or BFI questionnaires (all items scored on 0-10 NRS scales) failed to show significant burosumab/placebo differences, as follows:

The mean BPI Pain Severity score (a composite of worst/least/average/"right now" pain scores) was 4.9 and 5.2 in the placebo/burosumab groups at baseline. At week 24, the LS mean changes from baseline were -0.1 and -0.6 respectively, a nonsignificant difference.

The mean BPI Pain Interference score (the effect of pain on 7 daily activities) was 4.8 and 5.2 in the placebo/burosumab groups at baseline. At week 24, the LS mean changes from baseline were -0.4 and -0.5 respectively, a nonsignificant difference.

The mean BFI Worst Fatigue score (like BPI items, based on 24-hr recall) was 6.7 and 6.9 in the placebo/burosumab groups at baseline. At week 24, the LS mean changes from baseline were -0.5 and -0.7 respectively, a nonsignificant difference.

The mean BFI Global Fatigue score (a composite of 9 items related to fatigue severity and interference with daily activities) was 4.9 and 5.4 in the placebo/burosumab groups at baseline. At week 24, the LS mean changes from baseline were -0.03 and +0.04 respectively, a nonsignificant difference.

Pain medication use (evaluated using an exploratory analysis - not a prespecified endpoint):

The daily diaries used by patients for 7 days prior to visits (at baseline, weeks 12 and 24) included, in addition to BPI and BFI questions, a log of all oral pain medications taken on each day, including the number of doses. The data were summarized in Table 10.2.6.1 in the CSR. At baseline, 69% of subjects in the burosumab group and 67% of subjects in the placebo group were receiving pain medication, with 25% and 20%, respectively, receiving opioids. The use of pain medication overall and by type of pain medication remained relatively steady through the double-blind placebo-controlled portion of the study. At week 24, 66% of subjects in the burosumab group and 61% of subjects in the placebo group were receiving pain medications, with 24% and 21%, respectively, receiving opioids.

FDA Analysis of Pain Medication Use

To more fully understand pain medication usage during burosumab treatment, FDA conducted a descriptive analysis of opioid pain medication use in Study CL303, expressed in morphine milligram equivalent units.

Table 71 below presents opioid pain medication use status at baseline and at Week 24.

Table 71 Study CL303: Opioid Use Status at Baseline and Week 24

Baseline / Week 24 Opioid Use Status	KRN23 (n=68)	Placebo (n=66)
No / No	48 (70.6%)	48 (72.7%)
No / Yes	3 (4.4%)	5 (7.6%)
Yes / No	4 (5.9%)	4 (6.1%)
Yes / Yes	13 (19.1%)	9 (13.6%)

Source: Statistical reviewer's listing.

Subjects Who Did Not Use Opioids at Both Baseline and Week 24

Most subjects in both treatment groups did not use opioids at both baseline and Week 24: 70.6% of burosumab subjects and 72.7% of placebo subjects.

Subjects Who Did Not Use Opioids at Baseline and Did Use Opioids at Week 24

There were not many subjects who did not use opioids at baseline but used them at Week 24: 4.4% of burosumab subjects and 7.6% of placebo subjects.

Both groups had a mean morphine milligram equivalent (MME) increase from baseline: 3.5 MME for burosumab subjects and 12.8 MME in placebo subjects.

Subjects Who Used Opioids at both Baseline and Week 24 and Subjects Who Used Opioids at Baseline and Not at Week 24

The more relevant groups that provide information about a change in existing opioid use are the group who used opioids at both baseline and Week 24 (19.1% of burosumab subjects and 13.6% of placebo subjects) AND the group that used opioids at baseline and not at Week 24 (5.9% of burosumab subjects and 6.1% of placebo subjects).

Combining both groups, results in the following percentages:

25.0% of burosumab subjects and 19.7% of placebo subjects used opioids at baseline.

The following two tables present descriptive statistics for the mean MME change from baseline at Week 24 for the two use groups described above.

Table 72 presents the analysis for those subjects who used opioid pain medication at both baseline and at Week 24.

Table 72 Study CL303: Mean Change From Baseline to Week 24 in Morphine Milligram Equivalent For Subjects Who Used Opioids at Baseline and at Week 24

	Burosumab (n=13)	Placebo (n=9)	Difference (KRN23-Placebo)
Baseline	19.2	35.8	
Mean Change	1.9	-1.5	3.4
95% Confidence Interval	(-3.3, 7.0)	(-9.8, 6.9)	(-5.3, 11.9)

Source: Statistical reviewer's calculations, Descriptive Statistics

Table 73 presents the analysis for the combined group of those subjects who used opioid pain medication at both baseline and at Week 24 and those subjects who used opioid pain medication at baseline and not at Week 24, that is, all subjects who used opioids at baseline.

Table 73 Study CL303: Mean Change From Baseline to Week 24 in Morphine Milligram Equivalent For All Subjects Who Used Opioids at Baseline

	Burosumab (n=17)	Placebo (n=13)	Difference (KRN23-Placebo)
Baseline	20.8	26.8	
Mean Change	-4.7	-3.1	-1.6
95% Confidence Interval	(-16.7, 7.3)	(-8.7, 2.6)	(-15.7, 12.4)

Source: Statistical reviewer's calculations, Descriptive Statistics.

Note that all confidence intervals include zero.

As an example, the lowest dose marketed OxyContin ER pill is 10 mg and has an MME of 15. All MME mean values presented in the two tables above are less than 1/3 of a 10 mg OxyContin ER pill and the largest/smallest value of all the confidence interval limits is -16.7 MME or about one 10 mg OxyContin ER pill.

After evaluation of this data, it appears that there is insufficient evidence to support that burosumab decreases use of pain medication during therapy. It is possible that as longer term data is collected, a significant reduction in pain medication may become evident.

Secondary PD endpoints

Consistent with other studies, burosumab significantly increased serum 1,25(OH)₂D levels from baseline at week 22 (mid-dose interval) and reduced renal phosphate wasting as shown by significant increases from baseline in TmP/GFR and TRP compared to placebo at week 24 (end of dose interval).

Table 74 Study CL303: Secondary PD Endpoints, Change from Baseline and Percent Change from baseline at Week 22 or 24* – (PAS)

Secondary PD Endpoint	Statistics	Placebo (N = 66)	KRN23 (N = 68)
Serum 1, 25(OH)₂D			
Baseline	Mean (SD)	33.5 (15.6)	32.4 (13.0)
Change from baseline	LS Mean (SE) Difference vs. placebo 95% CI	2.7 (2.8)	25.5 (3.5) 22.7 (2.4) (18.0, 27.4)
% Change from Baseline	LS Mean (SE) Difference vs. placebo 95% CI	19.3 (14.3)	100.9 (17.8) 81.6 (11.7) (58.8, 104.5)
Ratio (TmP/GFR)			
Baseline	Mean (SD)	1.60 (0.37)	1.68 (0.40)
Change from baseline	LS Mean (SE) Difference vs. placebo 95% CI	0.13 (0.09)	0.56 (0.11) 0.43 (0.07) (0.29, 0.56)
% Change from Baseline	LS Mean (SE) Difference vs. placebo 95% CI	7.40 (5.12)	35.8 (6.13) 28.37 (4.35) (19.84, 36.89)
Tubular reabsorption of phosphate (TRP)			
Baseline	Mean (SD)	0.81(0.08)	0.81 (0.08)
Change from baseline	LS Mean (SE) Difference vs. placebo 95% CI	-0.01 (0.01)	0.03 (0.01) 0.04 (0.01) (0.02, 0.07)
% Change from Baseline	LS Mean (SE) Difference vs. placebo 95% CI	-1.12 (1.63)	4.68 (1.23) 5.79 (1.71) (2.44, 9.15)
*Post-baseline data are at week 22 for serum 1,25(OH) ₂ D, and at week 24 for TmP/GFR and TRP LS means and p-values are from the generalized estimation equation (GEE) model Source: CSR Table 14.2.3.2, Table 14.2.3.3, Table 14.2.3.11			

Bone turnover markers

Serum P1NP levels increased from baseline at week 24 by an LS mean of 74% in the burosumab group, compared to 8% in the placebo group. Serum CTX levels increased from baseline at week 24 by an LS mean of 38% in the burosumab group, compared to 11% in the placebo group.

Reviewer Comments:

As in study CL201, the applicant believes that increases in bone turnover may indicate an improvement in bone metabolism, i.e. replacement of osteoid by mineralized bone, but this hypothesis is not proven from the data in this submission.

Healing of pseudofractures and fractures

Active pseudofractures and fractures identified on the baseline skeletal surveys were followed up with targeted radiographs at weeks 12 and 24 to assess healing, an exploratory endpoint. During analyses, the applicant discovered that the two central readers had, in some instances, used the week 12 radiograph as the comparator for week 24. Thus, following re-training of the two readers, the week 24 radiographs were re-read with comparison to baseline, and the amended data, which were submitted on 12/7/17 (eCTD #0022), were used for the following discussion (3 other errors were discovered and also corrected during this process).

As outlined in the table below, active fractures and pseudofractures were present at baseline in 16 (12%) and 63 (47%) of study CL303 patients respectively. Nearly all fractures and pseudofractures involved the femur, tibia, fibula and/or foot (metatarsals); the most common locations were tibia/fibula for fractures, and femur for pseudofractures. At week 24, 50% of active fractures in the burosumab group had healed fully, compared with none in the placebo group. Similarly, 41% of baseline active pseudofractures in the burosumab group were fully healed at week 24, compared with 9% in the placebo group.

Table 75 Study CL303: Active fracture and pseudofracture healing over time (PAS)

	Active fractures		Active pseudofractures		Total	
	Placebo N=66	Burosumab N=68	Placebo N=66	Burosumab N=68	Placebo N=66	Burosumab N=68
# of active fracture/ pseudofractures at baseline	13	14	78	51	91	65
Week 12 Grade -n (% baseline)						
Healed	0	2 (14)	7 (9)	11 (22)	7 (8)	13 (20)
Partially healed	2 (15)	8 (57)	22 (28)	18 (35)	24 (26)	26 (40)
Week 24 Grade -n (% baseline)						
Healed	0	7 (50)	7 (9)	21 (41)	7 (8)	28 (43)
Partially healed	6 (46)	3 (21)	19 (24)	13 (26)	25 (28)	16 (25)
# of patients with active fracture/ pseudofractures at baseline	8	8	34	29	38	32
Week 12 Grade -n (% baseline)						
Healed	0	2 (25)	5 (15)	10 (35)	5 (13)	10 (31)
Partially healed	2 (25)	5 (63)	16 (47)	15 (52)	17 (45)	19 (59)
Week 24 Grade -n (% baseline)						
Healed	0	4 (50)	5 (15)	15 (52)	5 (13)	16 (50)
Partially healed	4 (50)	3 (38)	16 (47)	10 (35)	19 (50)	13 (41)

Source: Week 24 CSR Erratum submitted 12/7/17, Table 10.4.1.1.1

Imaging at weeks 12 and 24 was limited to skeletal regions with fractures or pseudofractures identified on the initial skeletal survey; therefore, new abnormalities could only be detected if located in one of the same regions. At week 12 there were 8 new findings in placebo patients (2 fractures, 6 pseudofractures) and 3 new pseudofractures in burosumab patients. At week 24 there were 3 new findings in burosumab patients (1 fracture, 2 pseudofractures) and none among placebo patients.

Reviewer Comments:

The post hoc correction of these data is acceptable from a clinical standpoint, and do not change any of the conclusions.

Patients with baseline fractures or pseudofractures (combined) were similar to the overall study population in BPI-Q3 pain scores at baseline and experienced similar score declines from baseline at week 24 (table below). The group of 21 patients with baseline fractures or pseudofractures that had fully healed at week 24 (disappearance of fracture lines) had a slightly larger decline in mean pain score compared to the 49 patients with baseline lesions that had not fully healed (-1.08 vs. -0.64).

Patients with baseline active fractures (fracture line at both cortices, n=16) also were similar to the overall study population in baseline pain scores (Table 76 below). Within this group, burosumab recipients had somewhat larger mean declines in pain score than the overall study. Improvements in pain scores were inconsistent, as shown by the following 4 patients who had baseline fractures that fully healed:

- # (b) (6): a 38 y/o female with baseline active fractures of tibia/fibula shaft and second metatarsal experienced healing at both sites at week 24, as well as healing of 3/4 active pseudofractures present at baseline (the fourth was partially healed); BPI-Q3 score declined from 7.4 to 4.5
- # (b) (6): a 48 y/o female experienced healing of two metatarsal lesions (one active fracture, one active pseudofracture) and partial healing of pseudofractures of the L femoral neck and R femoral mid-shaft; BPI-Q3 score declined from 7.1 to 6.1
- # (b) (6): a 45 y/o male had healing of a baseline distal tib/fib fracture, partial healing of a metatarsal fracture; and 3 baseline pseudofractures that were partially healed, unchanged or worse; BPI-Q3 score increased from 8.3 to 8.8
- # (b) (6): a 59 y/o female had 5 metatarsal fractures, 4 of which healed while the other was partially healed; and 1 metatarsal pseudofracture that healed; BPI-Q3 score declined from 7.4 to 2.3

Table 76 Study CL303: BPI Worst Pain score, by fracture/pseudofracture status

	Placebo	Burosumab	Overall
All patients, N	66	68	134
Baseline BPIQ3 score, mean	6.55	6.81	6.68
Week 24, mean	6.07	5.84	5.95
Mean change from baseline	-0.48	-0.97	-0.73
Treatment group difference	-0.49		
Patients with fractures or pseudofractures at baseline, n	38	32	70
Baseline BPIQ3 score, mean	6.85	6.61	6.74
Week 24, mean	6.30	5.57	5.97
Mean change from baseline	-0.55	-1.04	-0.77
Treatment group difference	-0.49		
Patients with fractures or pseudofractures at baseline that were fully healed at week 24, n	5	16	21
Baseline BPIQ3 score, mean	6.25	6.98	6.81
Week 24, mean	5.58	5.78	5.73
Mean change from baseline	-0.68	-1.20	-1.08
Treatment group difference	-0.52		
Patients with fractures at baseline, n	8	8	16
Baseline BPIQ3 score, mean	6.95	6.36	6.66
Week 24, mean	6.92	4.42	5.67
Mean change from baseline	-0.03	-1.94	-0.98
Treatment group difference	-1.91		
Patients with fractures at baseline that were fully healed at week 24, n	0	4	4
Baseline BPIQ3 score, mean	N/A	7.53	7.53
Week 24, mean	N/A	5.41	5.41
Mean change from baseline	N/A	-2.13	-2.13
Source: Week 24 CSR Erratum submitted 12/7/17, Listing 16.2.6.9.3 and amended adxray dataset; and original BLA adbpi dataset			

Reviewer Comments:

Active fractures and pseudofractures were identified at baseline in large numbers of adult XLH patients (inactive lesions that had healed prior to baseline, which were not followed up for changes, were also highly prevalent). Burosumab appears to promote the healing of these radiographic lesions compared to placebo; the clinical significance of this finding is unclear. The presence of pseudofractures and fractures had no apparent relationship with pain scores at baseline, and radiographic healing was not a strong predictor of pain improvement. This is consistent with the concept that bone/joint pain in XLH is complex and may result from many

factors, including osteoarthritis and enthesopathy in addition to osteomalacia with pseudofractures and fractures. Nevertheless, these outcome assessment endpoints provide supportive evidence of an improvement in the bone disease, most likely representing a reduction in osteomalacia.

Calcaneal Enthesopathy Burden

Another exploratory endpoint was the sum of the lengths of superior and inferior calcaneal spurs. There were baseline data on all patients from the skeletal survey, but week 24 data only on 22 patients because this was added in a protocol amendment. The calcification parameter decreased slightly in the placebo group (trend of improvement) and increased slightly in the burosumab group (trend of worsening); the difference between groups was not significant.

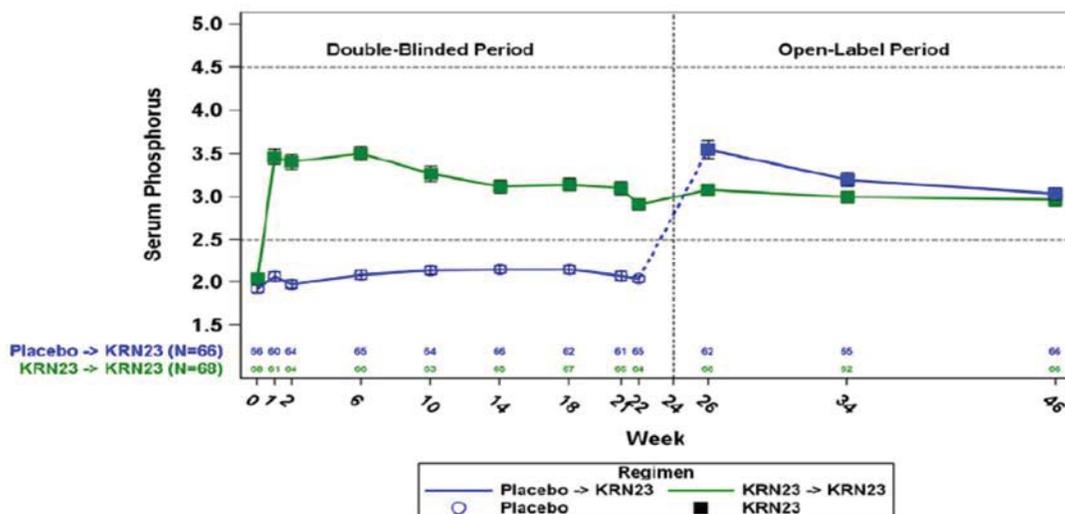
6-Minute Walk Test

The 6MWT was conducted at baseline, weeks 12 and 24 as another exploratory endpoint. Mean distance walked increased slightly from baseline in the burosumab group and decreased slightly in the placebo group; differences were not significant.

Durability of Response

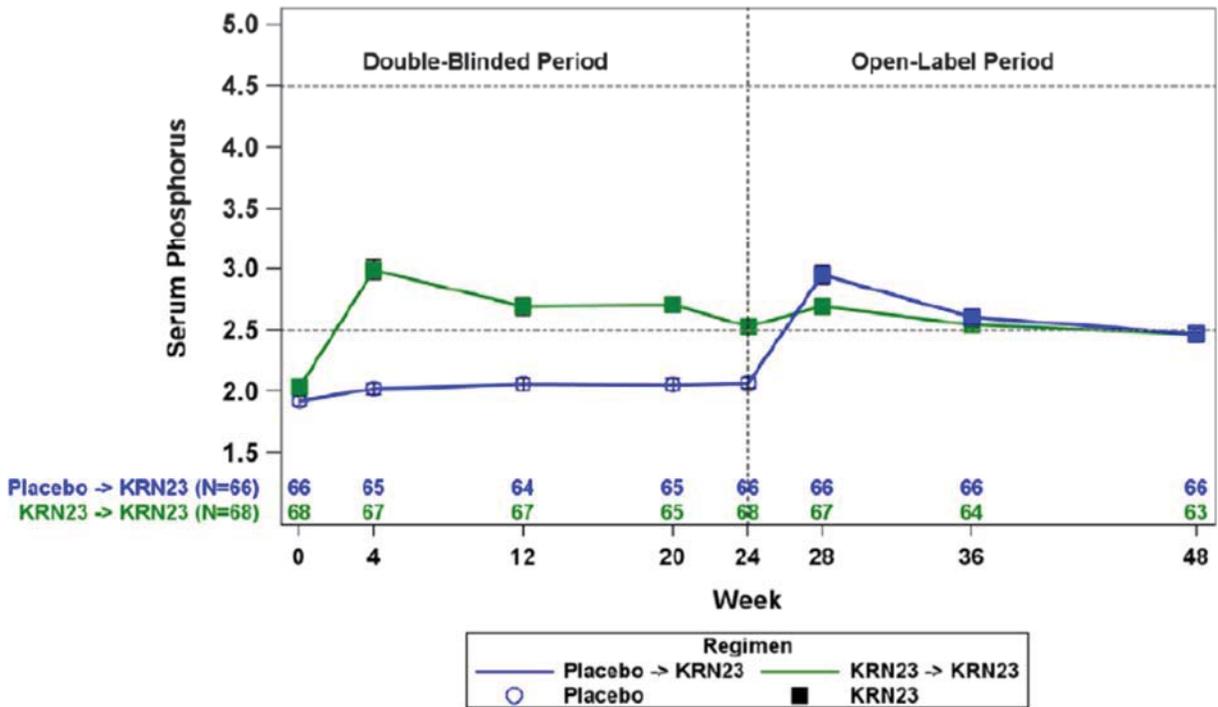
Figures 46 and 47 below depict serum phosphorus levels, at midpoint and end of dosing cycles respectively, through week 48 (patients in placebo arm received their first burosumab dose at week 24). Serum phosphorus increases were maximal following the first two doses of burosumab, then appeared to wane somewhat but stabilize after week 12-14:

Figure 46 Study CL303: Mean serum phosphorus (mg/dL) at midpoint of dose cycles (PAS)



Source: response to IR submitted 12/22/17. Dotted line represents LLN in adults (2.5 mg/dL)

Figure 47 Study CL303: Mean serum phosphorus (mg/dL) at end of dose cycles (PAS)



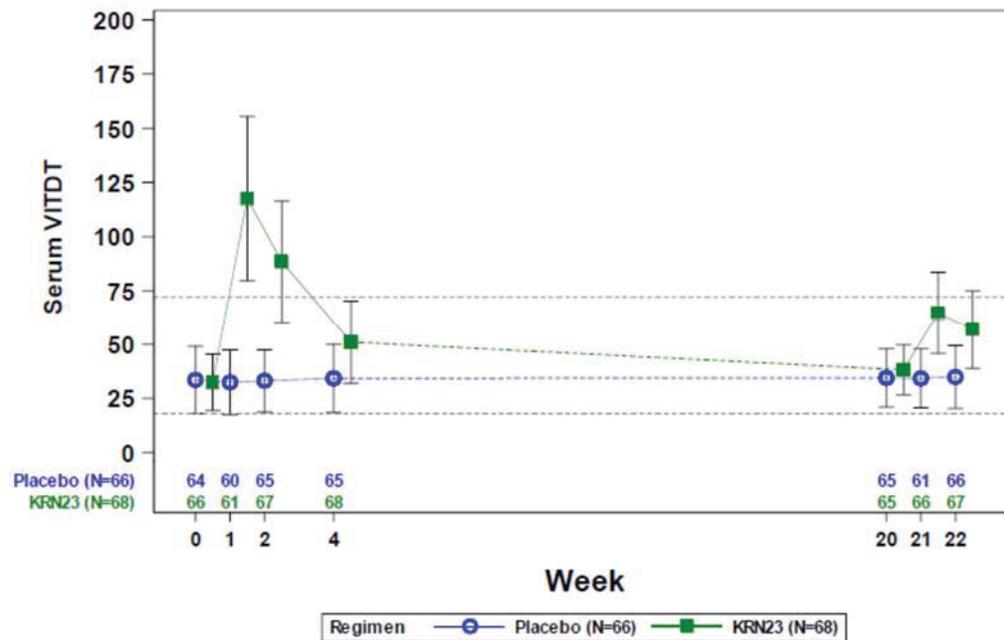
Source: response to IR submitted 12/22/17. Dotted line represents LLN in adults (2.5 mg/dL)

Reviewer Comments:

In this study as in study CL205 (see above), increases from baseline in serum phosphorus were slightly greater with the first one or two doses of burosumab than with subsequent doses. This did not occur in study CL201 because starting doses of burosumab were low. In each study however, serum phosphorus eventually stabilized at levels well above baseline.

In regard to serum 1,25(OH)vitamin D, levels were substantially higher 1-2 weeks after the initial dose of burosumab, compared to 1-2 weeks after the week-20 dose:

Figure 48 Study CL303: Mean (SD) serum 1,25(OH)₂D level (pg/mL) over time (PAS)



Source: Fig. 14.2.3.2.1.99.1 submitted on 1/17/18. Dotted lines represent normal range (18-72 pg/mL)

Reviewer Comments:

In the earlier study INT-002, there was a clear trend of progressively smaller 1,25(OH)₂D increases from baseline over 48 weeks of treatment, with levels above the normal range after the first few doses of burosumab but generally normal thereafter (CSR, Fig. 11.4-3). Study CL303 appears to confirm the attenuation of this particular PD effect over time. The pediatric studies CL201 and CL205 also suggested such an effect, but sampling points were limited in CL205. The applicant believes that this trend in 1,25(OH)₂D reflects improving calcium/phosphate homeostasis with continued burosumab therapy.

8.1.5. Study UX023-CL304

Study title: An Open-Label, Single-Arm, Phase 3 Study to Evaluate the Effects of KRN23 on Osteomalacia in Adults with X-linked Hypophosphatemia (XLH)

Overview and Objective

The primary efficacy objective of this study is to establish the effect of burosumab on XLH-associated osteomalacia, defined by bone biopsy-derived histomorphometry parameters, in adult patients.

Study Design

This single arm, multicenter phase 3 study was planned to enroll ~14 adult patients with XLH. All patients receive open label burosumab 1.0 mg/kg SC Q4W (rounded to nearest 10 mg, max 90 mg), with dose adjustment if needed for hyperphosphatemia, i.e. the same regimen used in study CL303. Also as in that study, vitamin D supplements are provided if 25(OH)D level drops below 20 ng/mL. Bone biopsies were performed at baseline and week 48, the time of the primary analysis. Study completers may enroll in an extension. The study is conducted at centers in the U.S. Japan, S. Korea, Denmark and France.

Study Population

The study population is intended to closely resemble that of study CL303 (see enrollment criteria for CL303 listed above, section 8.1.4), i.e. adults age 18-65 y/o with XLH; *PHEX* mutation or elevated serum FGF23; low serum phosphorus and TmP/GFR; and significant bone or joint pain at baseline (BPI-Q3 score ≥ 4). The main difference from CL303 is that, in order to avoid the confounding effects of conventional therapy on bone tissue, participants who had used oral phosphate and/or active vitamin D within 2 years were not eligible (compare to a 2-week washout in study CL303).

Study Assessments

Patient visits are scheduled every 2-4 weeks from baseline to week 48. Most of the lab monitoring for efficacy and safety is similar to study CL303, including assessments of ectopic mineralization (renal ultrasound and echocardiogram) and pregnancy testing.

Double-labeled bone biopsies of the iliac crest were performed at baseline and week 48 visits. Each biopsy was preceded by tetracycline or demeclocycline taken on days -20, -19, -18, -6, -5 and -4. Fixed biopsy samples were sent to (b) (4) for analysis, including routine histology and quantitative histomorphometry.

As in study CL303, a skeletal survey was conducted at baseline, and any active pseudofractures seen are followed up with targeted x-rays at 12-week intervals, as an exploratory efficacy endpoint.

The BPI and BFI questionnaires for patient-reported pain and fatigue are administered, but because of the open label study design, are designated as exploratory endpoints. The WOMAC is not included in this study.

Study Endpoints

Primary efficacy endpoint: Osteoid volume (OV/BV)

The primary endpoint, reflecting the characteristic excess of unmineralized osteoid in osteomalacia, is the percent change from baseline to week 48 in osteoid volume as a

proportion of bone tissue volume (OV/BV), based on analysis of iliac crest bone biopsies by histomorphometry. Osteoid normally constitutes less than ~3-4% of bone tissue; OV/BV >10% is consistent with osteomalacia. The other standard indices used to assess osteomalacia (O.Th, OS/BS and MLt, see below) were listed with OV/BV as primary endpoints in the original protocol, but were reassigned as secondary endpoints in amendment 2. The rationale provided for this change was that osteoid volume is the “most consistent” parameter for osteomalacia as it combines osteoid thickness and surface into one measure.

Secondary and other efficacy endpoints

Secondary endpoint: Serum phosphorus

Similar to the primary endpoint of CL303, this is the proportion of subjects with mean fasting serum phosphorus >LLN (2.5 mg/dL) at the mid-point of dose intervals, in this case weeks 2, 6, 14 and 22.

Other efficacy endpoints

Bone histomorphometry parameters:

- Osteomalacia: Osteoid thickness (O.Th), which is the average width of osteoid seams, and osteoid surface (OS/BS), which is the proportion of bone surface covered in osteoid, complement the osteoid volume (OV/BV) in detecting excess accumulation of osteoid. Osteoid thickness is normally ~4-12 µm; higher values are consistent with osteomalacia. Mineralization lag time (MLt) is the average time interval between osteoid formation and its subsequent mineralization, derived from the distance between two sequential tetracycline labels relative to the osteoid thickness; prolonged MLt > 100 days is considered to indicate osteomalacia. Percent changes from baseline to week 48 in O.Th, OS/BS and MLt will be used as secondary endpoints.
- Other mineralization parameters: mineral apposition rate (MAR), mineralizing surface (MS/BS) and bone formation rate (BFR), which are decreased in osteomalacia, and other histomorphometry parameters (change from baseline to week 48)

Additional serum phos-related endpoints: these are identical to secondary endpoints in study CL303, involving midpoint and trough levels and AUC (section 8.4.1)

Serum 1,25(OH₂D, urinary phos, TmP/GFR, TRP and serum P1NP, CTX, BALP (changes and/or percent changes from baseline): These are also identical to secondary PD endpoints in study CL303.

Statistical Analysis Plan

Sample size

The sponsor planned to enroll approximately 14 adult patients with XLH.

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Interim Analysis

The primary efficacy analysis was planned to be performed after all subjects completed Week 48 or discontinued from the study prior to week 48 and completed the post-baseline bone biopsy for those who had been determined to have osteomalacia at baseline.

The final analysis was to be performed after all subjects completed the Week 96 assessments and the Safety Follow-up or discontinued from the study.

Analysis Population

The sponsor pre-defined the following analysis populations:

- Primary analysis set: all enrolled subjects with baseline and follow-up (Week 48/ET) bone biopsy data.
- Full analysis set for efficacy: all enrolled subjects who received at least one dose of study drug. This analysis was used for the analyses of efficacy endpoints.
- Safety analysis set: all enrolled subjects who receive at least one dose of study drug. This analysis set was used for the analyses of all safety endpoints.
- Pharmacokinetics (PK) analysis set: subjects in the Safety analysis set who had at least 1 evaluable burosumab concentration. The PK analysis set was used for the analysis of the PK endpoints at each specific analysis milestone.

Handling of Missing and Incomplete Data

For all analyses, missing data were treated as missing, unless otherwise specified. When a change from baseline is assessed, only subjects with a baseline and at least one post-baseline measurement were included in the analysis.

If no serum data are available to evaluate the secondary endpoint, the subject was considered as not achieving a serum phosphorus level above the LLN.

Multiplicity Control

No multiplicity control was done for this study.

Efficacy Analysis Methods

Study CL304 was on going at the time of BLA submission and preliminary results were submitted for review. The primary endpoint is the percent change from baseline at Week 48 in osteoid volume (osteoid volume/bone volume, OV/BV). OV/BV at baseline, Week 48, both change from baseline, and percent change from baseline at Week 48 are summarized using descriptive statistics.

For other histomorphometric parameters – including osteoid thickness (O.Th), osteoid surface/bone surface (OS/BS), and mineralization lag time (MLt), and MAR, MS/BS, BFR and additional measures of bone formation and remodeling, the observed, change from baseline,

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and percent change from baseline values over time for the following parameters are summarized using descriptive statistics.

Protocol Amendments

The original protocol was dated 6/19/2015.

Protocol amendment 1 (3/29/2016) expanded the projected enrollment from ~10 to ~14 patients, and broadened the entry criteria (age 25-65 yr changed to 18-65 yr; and baseline serum iPTH $\geq 1.5 \times \text{ULN}$ changed to $\geq 2.5 \times \text{ULN}$).

Amendment 2 (10/7/2016) reassigned some of the osteoid related endpoints as discussed above, and added a 48 week study extension.

Amendment 3 (8/29/2017) added another extension for US patients, approx. 45 weeks through Sept. 2018.

Study Results

The original BLA included a brief interim report of this ongoing study (dated 7/26/2017) with preliminary biopsy data on 11 patients at baseline and 2 patients at week 48. Because of the importance of osteomalacia data to the application, DBRUP advised the applicant to submit any biopsy data as soon as it is available. Accordingly, additional interim reports (dated 10/12/2017 and 2/5/2018) were submitted, with week 48 biopsy data on a total of 11 patients.

Demographics and histomorphometry datasets were submitted on 2/23/2018. The full week-48 study report, to include results for other efficacy and safety endpoints, is not expected to become available during the review cycle.

Compliance with Good Clinical Practices

The brief interim reports include a statement that the study was performed in compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements.

Financial Disclosure

Study CL304 is among the covered clinical studies, as defined by 21 CFR 54.2(e), which provide the primary evidence establishing the effectiveness and safety of burosumab (see Appendix 15.2). The applicant has adequately disclosed financial interests/arrangements with the clinical investigators as recommended in FDA guidance, and no concerns are raised about the integrity of the data.

Patient Disposition

A total of 14 patients enrolled in this study. One patient withdrew consent, and the other 13 were continuing in the study as of the 2/5/2018 interim report. Biopsies were evaluable at baseline and week 48 for 11 patients. The other 3 baseline biopsies were obtained but not adequate for histomorphometry due to fragmentation, inadequate fixation and/or poor labeling quality; these patients did not undergo the second biopsy. Most of the patients (9/14)

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were enrolled at 2 centers in the US (sites #138-Yale and #139-UCSF). One patient enrolled at a center in France (site #186) and 4 patients at centers in Japan; all 3 of the patients with non-evaluative biopsies were Japanese (at 3 different centers in Japan).

Demographic and Baseline Characteristics

The 14 enrolled patients are similar to those in study CL303 with respect to age (mean 40 y/o, range 25-52 compared to mean 40 y/o, range 19-66 in study CL303); gender (8F/6M vs. 87F/47M); race (9 white/ 4 Asian/ 1 other vs. 108/21/5); and ethnicity (13/14 non-Hispanic vs. 122/134).

Baseline serum phosphorus (mean 2.24 mg/dL, range 1.2-2.8) was somewhat higher than in study CL303 (mean 1.98 mg/dL, range 1.3-3.0). No information on baseline disease characteristics was submitted. All of the 11 patients with evaluable bone biopsies at baseline exhibited osteomalacia (see below).

Treatment Exposure

According to the interim reports, serum phosphorus increased “consistent with” the response in study CL303 (data not provided), with no instances of hyperphosphatemia, and all patients were continuing at the prescribed dose of 1.0 mg/kg Q4W (max 90 mg). No data were provided on compliance with treatment visits or concomitant medications.

Efficacy Results - Primary and Secondary Osteomalacia-related Endpoints

At baseline, all 11 evaluable patients had osteomalacia, with excess accumulation of unmineralized osteoid as assessed by osteoid volume (OV/BV, the primary endpoint), osteoid thickness (O.Th) and osteoid surface (OS/BS) in comparison to reference values in healthy postmenopausal women (table below). Mineralization lag time (MLt) was prolonged in 6 patients, also indicative of osteomalacia, and was not evaluable in 5 patients due to decreased mineralization and low tetracycline uptake. (In the final report, the applicant plans to calculate MLt using an established imputation technique.)

Table 77 Study CL304: Summary of histomorphometry parameters at baseline

	Burosumab Evaluable at baseline N=11	Reference Values N=30-34*
Osteoid Volume/Bone Volume (OV/BV [%]), n	10	
Mean (SD)	26.1 (12.4)	1.9 (1.1)
Min, Max	8.8, 49.9	0.3, 3.1
Osteoid thickness (O.Th [μ m]), n	11	
Mean (SD)	17.2 (4.1)	9.3 (2.1)
Min, Max	12.1, 24.7	5.5, 12.0
Osteoid Surface/Bone Surface (OS/BS [%]), n	11	
Mean (SD)	91.7 (3.4)	14.3 (6.3)
Min, Max	85, 97	7.0, 25.0
Mineralization Lag Time (MLt [days]), n	6	
Mean (SD)	593.6 (675.2)	50.2 (41.9)
Min, Max	129.6, 1544.5	15.0, 50.0
* Recker RR, <i>J Bone Miner Res</i> (1988), 3: 133 (on healthy postmenopausal women) Source: 10/12/2017 Interim report, Table 2		

The 2/5/2018 interim report provides paired biopsy data (baseline and week 48) on the 11 evaluable patients (Table 78 below). There were substantial decreases from baseline in osteoid volume, thickness and surface (OV/BV, O.Th, OS/BS) in each patient (except patient # (b) (6) for whom baseline OV/BV could not be calculated), with overall mean declines of 57%, 33% and 26% respectively. Post-treatment values remained above reference range for OV/BV (with caveat that reference values were from an older patient population), but were mostly in normal range for O.Th. MLt was not evaluable at baseline for 5 of the patients but was measurable in 10/11 at week 48; MLt declined in 4 of the 6 paired specimens, with a mean change of -74%.

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Table 78 Study CL304: Histomorphometry parameters for available pairs, baseline and week 48

Patient number		(b) (6)											Overall Mean (SD)
Age/race/sex		24WF	37WF	31WF	39WM	32BM	38WM	28WF	46WF	50WF	49WM	49AsianF	
OV/BV (%)	Baseline	24.3	28.5	15.9	49.9	18.4	28.7	19.9	8.8	43	23.8	n/e	26.1 (12.4)*
	Week 48	8.6	7.4	9.2	8.2	3.2	14.8	13.7	5.1	25.6	16	18.6	11.2 (6.5)*
	% change	-65%	-74%	-42%	-84%	-83%	-48%	-31%	-42%	-40%	-33%	n/e	-57%*
O.Th (µm)	Baseline	19.4	16.2	14.3	24.7	17.1	23.3	13.1	12.1	19.6	15.1	14.4	17.2 (4.1)
	Week 48	12	7.2	11.4	13.7	9.2	18.6	9.9	8.7	14.1	11.5	10.8	11.6 (3.1)
	% change	-38%	-56%	-20%	-45%	-46%	-20%	-24%	-28%	-28%	-24%	-25%	-33%
OS/BS (%)	Baseline	96	92	97	90	92	92	93	90	94	88	85	91.7 (3.4)
	Week 48	74	54	73	65	34	74	80	63	81	73	75	67.8 (13.7)
	% change	-23%	-41%	-25%	-28%	-63%	-20%	-14%	-30%	-14%	-17%	-12%	-26%
MLt (days)	Baseline	226.4	n/e	n/e	1544.5	129.6	n/e	1378.4	148.9	133.5	n/e	n/e	593.6 (675.2)‡
	Week 48	117.6	242.6	255.8	69.8	76.7	n/e	238.3	228.5	202.7	241.1	281.9	155.6 (76.7)‡
	% change	-48%	n/e	n/e	-95%	-41%	n/e	-83%	+53%	+52%	n/e	n/e	-74%‡
*means and % change based on n=10 (excluding patient (b) (6)) ‡means and % change based on n=6 patients with evaluable MLt at baseline n/e = not evaluable Source: 2/5/18 interim report, Tables 3 and 4 and DM dataset													

Reviewer Comments:

Although there is no control group for bone biopsies, it is highly unlikely that these substantial improvements in osteomalacia would occur spontaneously in untreated adult XLH patients.

As noted in section 2.2, a prospective study of 6 adults with XLH treated with phosphate and calcitriol previously showed similar mean percent reductions in osteomalacia parameters (-50%, -47% and -29% for OV/BV, O.Th and OS/BS respectively) (Sullivan W et al, JCEM 1992, 75:879). However, responses were less consistent than in study CL304, with one patient showing essentially no change from baseline, and patients were treated for a longer period (mean 4.2 years). Moreover, the phosphate and calcitriol daily doses were substantially higher than current recommendations; subsequent to this publication, safety concerns (nephrocalcinosis and hyperparathyroidism) resulted in the currently recommended doses.

Efficacy Results - Secondary and other relevant endpoints

The submitted interim reports of study CL304 include only the limited data outlined above, with no information on other efficacy (serum phos and other PD) or safety endpoints.

Based on the submitted histomorphometry dataset, dynamic parameters of bone formation showed expected increases but were highly variable. Mineral apposition rate (MAR, $\mu\text{m}/\text{day}$) increased from baseline by a mean of 49% (range -66% to +157%). Mineralizing surface/ bone surface (MS/BS, %) increased from baseline by a mean of 105% (range -50% to +318%) in 10 evaluable patients. Bone formation rate/bone volume (%/yr) increased from baseline by a mean of 54% (range -72% to +300%) in 6 evaluable patients.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy across Trials

Clinical manifestations of XLH vary by age; the pediatric and adult populations endpoints were markedly different between studies CL205 and CL201 (age 1-4 years old and 5-12 years old respectively) and study CL303 (age 18-65 years old). Therefore, the assessment of burosumab efficacy is primarily based on review of the individual studies as discussed in section 8.1 above. However, because of the lack of controls in the pediatric studies, the comparison between study CL201 and the historical control study, CL002, is important to the assessment of pediatric efficacy and is discussed below.

Comparison to Conventional Therapy in Pediatric Patients

The sponsor assessed the treatment benefits of burosumab relative to conventional therapy by comparing the results from Study UX023-CL201 with those of Study UX023-CL002. Study UX023-CL002 employed a retrospective radiographic and chart review of patients with XLH who had received long-term conventional therapy with oral phosphate and active vitamin D. For the

radiographic analyses of rickets, subjects were required to have a minimum of two bilateral sets of wrist and knee x-rays taken 1 to 2 years apart (± 3 months) when the subject was between the ages of 5 and 14 years.

The following two approaches were pre-specified in the statistical analysis plan to compare the severity of rickets after treatment with burosumab (Study UX023-CL201) and after treatment with conventional therapy (Study UX023-CL002):

1. Comparing the change from baseline in RSS score after 64 weeks of treatment using the observed data in the two studies
2. Using Propensity Score methods to address imbalances between baseline characteristics in the two studies in the analyses of rickets assessments (RSS and RGI-C).

Reviewer Comments:

The sponsor's approaches were agreed to by the Agency after reviewing the submitted statistical analysis plan.

In Study UX023-CL002, a radiograph pair was defined as two radiograph sets from two time points that were 9 to 27 months apart. (A radiograph set was defined as a set of X-rays of the bilateral wrist and knee taken at the same time). When more than one evaluable radiograph pair was available for a subject, the pair with the duration between two radiographs closest to 64 weeks was selected. Baseline for a radiograph pair in Study UX023-CL002 was defined as the assessment at the time when the earlier set of bilateral wrists and knees X-rays were taken.

Analysis Population:

For Study UX023-CL002, in the 52 subjects who were on conventional therapy, only those who had evaluable radiograph pairs (bilateral wrist and knee X-rays, growth plates not fused or partially fused) were included in the analysis (n = 30).

For Study UX023-CL201, the RSS and RGI-C data collected at baseline and Week 64 in all subjects (two regimen groups were combined) from the ITT population were used. All subjects (n=52) were included in the analysis.

Statistical Methods:

For this comparison, the planned primary endpoints for this analysis were:

- Change from baseline in RSS total score at Week 64
- RGI-C global score at Week 64

The Propensity Score (PS) approach was used to generate a more comparable sample that would diminish the impact of selection bias on the comparison of the changes in RSS and RGI-C observed with burosumab and conventional therapy in Studies UX023-CL201 and UX023-CL002. PS is defined as the conditional probability of being treated with burosumab. For each subject,

the PS was estimated by a logistic regression model with the baseline RSS total score, age, and sex as covariates. The PS values were used for weighting or matching.

The following three methods were performed for the PS analysis:

- an Inverse Probability of Treatment Weighting (IPTW) method that included all subjects from both studies,
- a matching without replacement method that was randomly repeated 1000 times to allow for different subsets of subjects to be matched in each round, and
- a matching with replacement method that allowed one control to be matched to multiple treated subjects.

Demographics and baseline variables were summarized to examine the comparability between Study UX023-CL201 and Study UX023-CL002 cohorts after the propensity score approaches were applied.

After weighting or matching, an ANCOVA model (with baseline RSS total score as covariate and treatment group as factor) was used to estimate the difference between groups. The change from baseline in RSS total and RGI-C global scores in the burosumab group and in the conventional therapy group and the difference between the two groups were estimated; the corresponding 95% confidence intervals were provided. A descriptive summary was presented for the RSS and RGI-C wrist and knee scores.

Efficacy Results:

The patients enrolled in Study UX023-CL201 were older than those in Study UX023-CL002 (8.5 vs. 8.1 years old) and had a higher baseline level of rickets (i.e. higher RSS scores).

The PS was used to generate populations that were more comparable than the unweighted study population (see Table 79).

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Table 79: Demographics and Baseline Characteristics in Study UX023-CL201 (Burosumab Treatment) vs Study UX023-CL002 (Conventional Therapy) in Propensity Score Analyses

	Study Assessments (not weighted)		Weighted by Inverse Probability of Treatment ^a		Propensity Score Matching Without Replacement in Control ^b		Propensity Score Matching With Replacement in Control ^c	
	UX023- CL201 ^d	UX023- CL002 ^e	UX023- CL201 ^d	UX023- CL002 ^e	UX023- CL201 ^d	UX023- CL002 ^e	UX023- CL201 ^d	UX023- CL002 ^e
Sample size	52	30	52	30	29.7	29.7	52	29
Age at Baseline (mean [SD] years)	8.5 (1.9)	8.1 (2.1)	8.3 (1.7)	8.4 (2.5)	8.3 (1.9)	8.1 (2.0)	8.5 (1.9)	8.3 (2.9)
Sex (% female)	53.8%	63.3%	57.4%	54.7%	54.7%	63.6%	53.8%	50.0%
Age when Conventional Therapy Initiated (mean [SD] years)	2.1 (1.3)	2.1 (1.4)	2.1 (1.2)	2.0 (1.5)	2.0 (1.4)	2.1 (1.3)	2.1 (1.3)	1.8 (1.6)
Baseline RSS								
Wrist score (mean [SD])	0.60 (0.58)	0.40 (0.42)	0.49 (0.50)	0.55 (0.60)	0.34 (0.46)	0.40 (0.42)	0.60 (0.58)	0.57 (0.67)
Knee score (mean [SD])	1.20 (0.64)	0.83 (0.51)	1.07 (0.59)	1.01 (0.66)	0.93 (0.60)	0.84 (0.50)	1.20 (0.64)	1.07 (0.74)
Total score (mean [SD])	1.80 (1.09)	1.23 (0.81)	1.55 (0.8)	1.55 (1.13)	1.27 (0.92)	1.24 (0.79)	1.80 (1.09)	1.63 (1.25)

^a Burosumab subjects (Study UX023-CL201) receive a weight equal to 1/Propensity Score, and conventional therapy subjects (Study UX023-CL002) receive a weight equal to 1/(1-Propensity Score), where the propensity score is estimated from a logistic regression model with treatment group as response (1 = burosumab, 0 = conventional therapy), baseline RSS total score and age as covariates and sex as a categorical covariate.

^b Mean sample size and results based on 1000 iterations of PS matching without replacement.

^c A conventional therapy subject could be selected to match multiple treated subjects. Conventional therapy subjects matched multiple times received higher weights based on the number of times matched.

^d All subjects from the intent-to-treat (ITT) analysis set were selected.

^e All subjects from the radiograph analysis set were selected; when more than one radiograph pair available for a subject, the pair with the duration between two radiographs taken closest to 64 weeks is selected; radiographs that were deemed as growth plates fused or partially fused were excluded from the analysis.

Sources: Table 2.7.3.3.2.3.2 in summary-clin-efficacy-xlh.pdf.

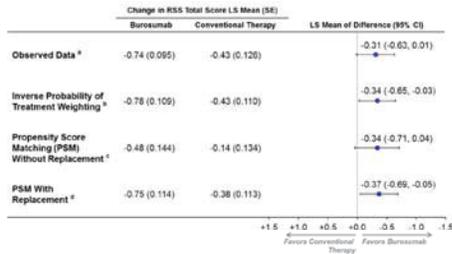
For the observed data analysis and all three PS analyses, the burosumab group had a greater decrease in change from baseline in RSS total score than did the conventional therapy group.

- For the observed data analysis, the LS mean (95% CI) estimated decrease in RSS total score was -0.74 (-0.93, -0.55) in the burosumab group compared to -0.43 (-0.68, -0.18) in the conventional therapy group; the difference between groups was -0.31 (-0.63, 0.01).

The three PS analyses showed similar differences in change from baseline in RSS total score between the burosumab and conventional therapy groups:

- For the IPTW analysis, the LS mean (95% CI) estimated decrease in RSS total score was -0.78 (-0.99, -0.56) in the burosumab group compared to -0.43 (-0.65, -0.22) in the conventional therapy group; the difference between groups was -0.34 (-0.65, -0.03).
- For the PS matching without replacement analysis, the LS mean estimated decrease in RSS total score was -0.48 (-0.75, -0.19) in the burosumab group compared to -0.14 (-0.40, 0.12) in the conventional therapy group; the difference between groups was -0.34 (-0.71, 0.04).
- For the PS matching with replacement analysis, the LS mean estimated decrease in RSS total score was -0.75 (-0.98, -0.52) in the burosumab group compared to -0.38 (-0.61, -0.16) in the conventional therapy group; the difference between groups was -0.37 (-0.69, -0.05).

Figure 49 - Differences in RSS Total Scores (LS Mean ± SE) Between Study UX023-CL201 (Burosumab Treatment) and Study UX023-CL002 (Conventional Therapy) from Propensity Score Analyses



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a n=52 burosumab, n=30 conventional therapy

b Burosumab subjects (Study UX023-CL201) receive a weight equal to 1/Propensity Score and conventional therapy subjects (Study UX023-CL002) receive a weight equal to 1/(1-Propensity Score), where the propensity score is estimated from a logistic regression model with treatment group as response (1= burosumab, 0 = conventional therapy), baseline RSS total score and age as covariates and sex as a categorical covariate.

c Summary based on 1000 iterations of PS matching without replacement.

d A conventional therapy subject could be selected to match multiple burosumab subjects. Conventional therapy subjects matched multiple times received higher weights based on the number of times matched.

Source: Figure 2.7.3.3.2.3.2 in summary-clin-efficacy-xlh.pdf.

The burosumab group had a greater increase in estimated RGI-C global score than did the conventional therapy group in the observed data analysis and all three PS analyses.

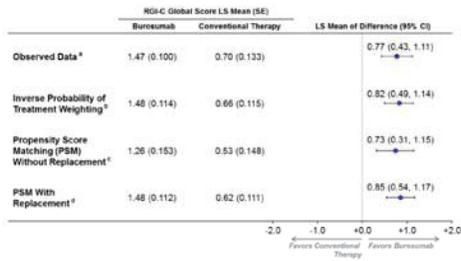
- For the observed data analysis, the LS mean (95% CI) estimated RGI-C global score was 1.47 (1.27, 1.67) in the burosumab group compared to 0.70 (0.43, 0.97) in the conventional therapy group; the difference between groups was 0.77 (0.43, 1.11).

The three PS analyses showed similar differences in RGI-C total score between the burosumab and conventional therapy groups:

- For the IPTW analysis, the LS mean (95% CI) estimated RGI-C global score was 1.48 (1.25, 1.70) in the burosumab group compared to 0.66 (0.43, 0.89) in the conventional therapy group; the difference between groups was 0.82 (0.49, 1.14).
- For the PS matching without replacement analysis, the LS mean estimated RGI-C global score was 1.26 (0.97, 1.57) in the burosumab group compared to 0.53 (0.24, 0.82) in the conventional therapy group; the difference between groups was 0.73 (0.31, 1.15).
- For the PS method with replacement analysis, the LS mean estimated RGI-C global

score was 1.48 (1.26, 1.70) in the burosumab group compared to 0.62 (0.40, 0.84) in the conventional therapy group; the difference between groups was 0.85 (0.54, 1.17).

Figure 50 - Differences in RGI-C Global Scores (LS Mean ± SE) Between Study UX023-CL201 (Burosumab Treatment) and Study UX023-CL002 (Conventional Therapy) from Propensity Score Analyses



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- a N=52 burosumab, 30 conventional therapy
 - b Burosumab subjects (Study UX023-CL201) receive a weight equal to 1/Propensity Score and conventional therapy subjects (Study UX023-CL002) receive a weight equal to 1/(1-Propensity Score), where the propensity score is estimated from a logistic regression model with treatment group as response (1= burosumab, 0 = conventional therapy), baseline RSS total score and age as covariates and sex as a categorical covariate.
 - c Summary based on 1000 iterations of PS matching without replacement.
 - d A conventional therapy subject could be selected to match multiple burosumab subjects. Conventional therapy subjects matched multiple times received higher weights based on the number of times matched.
- Sources: Figure 2.7.3.3.2.3.2 in summary-clin-efficacy-xlh.pdf.

These supportive analyses appear to demonstrate a trend that burosumab treatment results in a reduction in rickets severity as compared to conventional therapy given the limitation of using historical data for comparison.

Reviewer Comments:

Although the two study populations differed in some respects, the PS analyses improved their comparability. The consistent treatment group differences help support burosumab efficacy in XLH-rickets, and probably greater efficacy than conventional therapy. Eventually, a more direct comparison of these two treatments will be provided by the ongoing randomized phase 3 study,

CL301.

Additional Efficacy Considerations

Considerations on Benefit in the Postmarket Setting

The clinical studies did not enroll adolescents with XLH (age 13-17 inclusive), although the proposed indication includes this group. Because most of these patients have open growth plates, they should generally receive treatment similar to younger patients, including burosumab Q2W with dose guided by serum phosphorus levels. The pediatric and adult studies showed similar effects on phosphorus and other PD endpoints and favorable effects on skeletal endpoints; therefore, it is reasonable to expect significant treatment benefit in adolescents. This should be confirmed; the planned DMP postmarket study (section 12) will provide data in this age group from follow-up of study CL201 patients as well as XLH patients treated in routine postmarket prescribing.

Other Relevant Benefits

As described above, clinical studies of burosumab provide evidence of efficacy in pediatric and adult XLH populations, while efficacy of the current standard of care treatment (oral phosphate and active vitamin D) is not well established, especially in adult XLH patients. In addition to efficacy, burosumab offers other advantages that are relevant to clinicians and patients. Conventional therapy is inconvenient, requiring multiple daily doses of phosphate which may cause GI side effects, potentially affecting compliance, as well as frequent blood draws and timed urine collections. Burosumab will require frequent clinic visits for injections (b) (4) but these frequent visits probably help enforce adherence and allow additional long term data to be collected. Blood draws for monitoring treatment will be more limited with burosumab compared to conventional therapy, and timed urine collections unnecessary. In addition, it is likely that long term safety of burosumab will compare favorably to conventional therapy in regard to adverse effects of hyperparathyroidism and nephrocalcinosis (see safety review, section 8.3).

8.2.2. Integrated Assessment of Effectiveness

The fundamental goal of any XLH treatment is to correct hypophosphatemia, the underlying cause of all (or nearly all) of the clinical manifestations. Because of safety issues, current therapy (oral phosphate/active vitamin D) only partially corrects hypophosphatemia, which likely contributes to its limited efficacy. Burosumab was effective in normalizing serum phosphorus in children and adults with XLH. The skeletal manifestations of the disease differ in actively growing patients and adults; therefore, some of the objectives and endpoints of pediatric and adult studies are different.

Pediatric XLH

In children with XLH, evidence of efficacy is provided by studies CL201 (age 5-12 years) and CL205 (age 1-4 years). These studies were uncontrolled, primarily because the use of placebo was considered to be unethical in children with XLH, and the use of an active control (e.g. oral phosphate/calcitriol) would present potential difficulties in blinding, enrollment and other issues. Because of the lack of controls, a historical study in children age 5-14 years receiving conventional therapy (CL002) was conducted to provide comparison data for study CL201.

Study CL201

Study CL201 is an ongoing randomized, open-label, dose finding phase 2 study of pediatric XLH patients. The objectives are to identify a burosumab regimen (dose and interval) based on safety and PD effects, and to obtain a preliminary assessment of the effects of burosumab on bone health and other clinical outcomes. The study enrolled 52 children age 5-12 years old, Tanner stage ≤ 2 with open growth plates; the rationale for not including adolescents was that open growth plates are needed for optimal evaluation of rickets and growth. The entry criteria required an XLH diagnosis supported by either genetic testing (*PHEX* mutation) of the patient or a family member with X-linked inheritance, or a serum FGF23 level >30 pg/mL. Other criteria included a fasting serum phosphorus ≤ 2.8 mg/dL, normal serum creatinine, and radiographic evidence of active bone disease (for the initial 36 “pre-expansion” patients, rickets and/or femoral/tibial bowing; for the 16 “expansion” patients, a minimum radiographic rickets score of $RSS \geq 1.5$).

Patients in study CL201 were randomized to Q2 week versus Q4 week dosing (n=26 in each group). Starting doses were low (0.1-0.3 mg/kg Q2W or 0.2-0.6 mg/kg Q4W), with monthly adjustments aimed at achieving and maintaining a target range for serum phosphorus 2 weeks post dose of 3.5-5.0 mg/dL, which is approximately the low to middle portion of normal range for this age group. The maximum dose was 2.0 mg/kg or 90 mg. Concomitant treatment with oral phosphate or active vitamin D was not permitted; nutritional vitamin D was provided if serum 25(OH)vitamin D levels fell below 20 ng/mL.

Among the 52 patients randomized, 36 (69%) enrolled at one of 4 U.S. sites. There were 28 girls and 24 boys, with a mean age of 8.5 years; 89% were white and 96% were non-Hispanic. All except 2 of the children had been previously treated for XLH with conventional therapy, beginning at an average age of ~ 2 years and for an average duration of almost 7 years. Despite this treatment, patients exhibited at baseline significant growth delay (mean height Z-score -1.9) and most had significant radiographic rickets as well as a variety of lower extremity deformities that are typical of XLH, most commonly varus abnormalities with bowing of the femur and tibia.

All 52 patients have continued in the study and data were submitted through at least week 64. Following dose titration, steady state was reached at \sim week 40-64, with an average dose of ~ 1.0 mg/kg Q2W (range 0.4-2.0 mg/kg) or ~ 1.5 mg/kg Q4W (range 0.6-2.0 mg/kg). In the Q2W

group, mean serum phosphorus (the primary PD endpoint) had increased from 2.4 mg/dL at baseline to 3.3 mg/dL (normal range for age ~3.2-6.1 mg/dL) at steady-state. In the Q4W group, there was a peak-and-trough pattern in serum phosphorus, with pre-dose (trough) levels below normal range. In order to maintain normal phosphorus and, thereby, optimize skeletal benefits, Q4W patients were transitioned to Q2W dosing at week 64. Secondary PD endpoints, TmP/GFR and serum 1,25(OH)₂vitamin D, also showed substantial increases from baseline, reflecting the improvements in renal phosphate wasting and in 1 α -hydroxylase activity, respectively.

The primary efficacy endpoint of study CL201 was the radiographic Rickets Severity Scale (RSS) total score. The RSS, developed and validated for evaluation of nutritional rickets, evaluates the metaphyseal and growth plate abnormalities of rickets at the knee (distal femur and proximal tibia) and wrist (distal radius and ulna) and assigns a total RSS score of 0 (no rickets) to 10 (worst possible), and subscores of 0-6 for knee RSS and 0-4 for wrist RSS. Nearly all of the skeletal pathology of pediatric XLH results from rickets, and DBRUP accepts RSS as a clinically relevant endpoint in XLH. In order to ensure objective readings and RSS scores, images from study CL201 patients were intermixed randomly and blindly with those of other XLH patients, and the reader was also blinded to image sequence.

At baseline, the mean RSS total score for the overall study population (N=52) was 1.80. At weeks 40 and 64, LS mean changes from baseline were -0.89 (95% CI -1.04, -0.75) and -0.92 (-1.07, -0.78) (each p<0.0001). These correspond to 50% and 51% declines from baseline respectively. RSS mean declines were numerically greater in the Q2W group compared to the Q4W group (at week 64, -1.00 vs. -0.84). Patients with higher baseline RSS (≥ 1.5 , n=34) had larger declines (mean -1.44 at week 64) while patients with lower baseline RSS (<1.5, n=18) had little change from baseline (mean +0.06 at week 64). Analyses of other subgroups showed similar RSS declines in patients age 5-8 y/o vs. 9-12 y/o. Girls had slightly higher RSS mean at baseline compared to boys (1.96, 1.60) and also larger declines from baseline to week 64 (-1.27, -0.52). The small numbers of patients who were nonwhite (6) or Hispanic (2) precluded meaningful analysis by race or ethnicity. U.S. patients, compared to non-U.S. had similar baseline RSS (1.75, 1.91) and slightly larger declines at week 64 (-1.06, -0.63). RSS knee and wrist subscores, which were secondary endpoints, showed that rickets improvements were similar between these two skeletal sites.

The applicant also devised another scale, the Radiographic Global Impression of Change (RGI-C) to assess a variety of rickets features over time, with comparison of baseline and postbaseline images to yield a score ranging from -3 ("severe worsening") to +3 ("complete or near complete healing"), with 0 indicating no change. RGI-C scores for the knee, the wrist, a global score (knee and wrist combined) and for lower extremity deformities such as bowing (based on standing long leg radiographs) were prespecified as secondary endpoints. At week 64, mean RGI-C scores for the overall study were +1.55 (knee), +1.60 (wrist), +1.57 (global), and +0.47 (lower extremity deformities). The minimal change from baseline for the latter is not unexpected; past experience with nutritional rickets, and conventional therapy of XLH, has been that rickets

generally improves within ~6 months, while bowing and other deformities tend to improve over a longer time course, if at all.

Growth is another study CL201 secondary endpoint, primarily assessed by standing height Z-scores (age/gender adjusted). In the overall study, mean height Z-score was -1.89 at baseline; mean change from baseline at week 64 was +0.15 (95% CI, +0.08, +0.23).

Serum alkaline phosphatase (ALP), an indicator of rickets activity that is monitored by many treating clinicians, was elevated at baseline and declined substantially during the study, with mean levels of 459, 395 and 369 U/L at baseline, weeks 40 and 64 respectively (declines of 13% and 20% from baseline). This is supportive of improvement over the duration of burosumab treatment.

In addition to these week 64 data on all CL201 patients, the BLA includes week 88 data on the first 36 ("pre-expansion") patients enrolled. Improvements in rickets were maintained over time in this cohort: mean changes from baseline in RSS total score were -0.43, -0.56 and -0.54 at weeks 40, 64 and 88 respectively. Mean RGI-C global and lower extremity deformity scores at week 88 were +1.65 and +0.52, both increased slightly from week 64. Growth showed a continued trend of slight improvement: mean changes from baseline in height Z-score were +0.15, +0.16 and +0.21 at weeks 40, 64 and 88. Mean burosumab dose and mean serum phosphorus and TmP/GFR were stable through this period, indicating no evidence of loss of PD effects over time.

The main limitation of the evidence from study CL201 is the lack of control patients, particularly because standard of care treatment (phosphate/calcitriol) appears to have some efficacy (albeit limited) in XLH-associated rickets. The historical control study CL002 provides comparison data on 35 children age 5-14 y/o with XLH-rickets who were followed at one center while receiving oral phosphate and calcitriol. Although the study is retrospective, the data had been gathered prospectively (as part of a separate study) and included knee and wrist xrays at regular intervals regardless of clinical status. Radiographs from studies CL002 and CL201 were intermixed and assigned RSS and RGI-C scores for changes from baseline by the same radiologists, blinded to treatment. At the time of their baseline xray series, the control patients were generally similar demographically to CL201 patients, but more likely to be female (69% vs. 54%) and with less severe rickets (mean total RSS 1.4 vs. 1.8). In order to address the imbalances, the applicant used Propensity Score (PS) methods to compare data on 30 control patients who had x-ray pairs suitable for matching with the baseline/week 64 xray data from the 52 patients in CL201. The observed data showed a greater decline from baseline in RSS total score with burosumab compared to conventional therapy, with LS mean of the difference -0.31 (95% CI -0.63, 0.01). Three different PS approaches each yielded similar differences between the groups. For RGI-C global score, the observed data showed higher scores in the burosumab group compared to conventional therapy, with LS mean of the difference 0.70 (95% CI 0.43, 1.11); results with the 3 PS methods again showed similar findings. It should be noted that because Q2W efficacy with

burosumab was numerically greater than Q4W efficacy in study CL201, the PS analyses may underestimate the benefit of Q2W treatment. Although these comparisons are imperfect, they tend to support a conclusion that burosumab is more effective than conventional therapy in correcting rickets in the pediatric XLH population.

Study CL205

Study CL205 is an ongoing open label, phase 2 study in children with XLH age 1-4 years old. The primary objectives are to establish the safety profile and PD effects of burosumab in this age group; additional objectives are to assess the effects on rickets, growth and skeletal deformities. This study is of particular importance because most children with XLH are diagnosed within this age range, and because earlier initiation of conventional therapy for XLH has been shown to provide the best prognosis for long-term skeletal outcomes and growth.

Enrollment criteria included clinical findings consistent with XLH including hypophosphatemia (<3.0 mg/dL), radiographic evidence of rickets (at least 5 subjects with an RSS at the knee of ≥ 1.5 at screening), a confirmed *PHEX* mutation or variant of uncertain significance, and normal serum creatinine. Concomitant oral phosphate or active vitamin D was not allowed; vitamin D supplements were to be provided for serum 25(OH)D <20 ng/mL. All patients in this single-arm study received a starting dose of 0.8 mg/kg Q2W; one increase to 1.2 mg/kg Q2W was allowed if serum phosphorus remained below normal.

A total of 13 children at 3 U.S. centers are enrolled: 9 boys/ 4 girls; mean age 2.9 years; 12 white/1 black; 2 Hispanic. All patients had received conventional therapy, starting at an average age of 21 months. Mean baseline RSS score was 2.92 (range 1.0-6.5). All patients had leg bowing. Mean height (or recumbent length) Z-score was -1.38.

Serum phosphorus, the primary endpoint, increased from mean baseline of 2.5 mg/dL to 3.7 mg/dL after the first dose and remained above the LLN (3.2 mg/dL) through week 40. Three children underwent the protocol-driven dose increase to 1.2 mg/kg Q2W. At week 40 the mean administered dose was similar to that point in study CL201 (0.89 vs. 0.98 mg/kg Q2W) and the mean change from baseline serum phosphorus was also similar (0.96 vs. 0.92 mg/dL). Mean RSS total score declined, from baseline 2.92 to 1.19 at week 40 (LS mean change -1.73, 95% CI -2.03, -1.44), representing a 59% decline. Declines in mean RSS knee and RSS wrist subscores were similar. LS-mean RGI-C global score at week 40 was +2.33 (95% CI +2.16, +2.51). RGI-C lower limb deformity scores were >0 for all 13 patients at week 40, with LS mean of +1.26. Mean serum ALP declined from 549 U/L at baseline to 335 U/L at week 40, a 39% decline.

Mean height (or recumbent length) increased by 4.2 cm from baseline to week 40, but mean height Z-score declined from -1.38 to -1.65. The cause for this trend, which is contrary to the growth trend in older children (study CL201), is not clear; it may represent the typical drop-off from normal growth curves that occurs in children with XLH at this age. Because of the small sample size and limited duration of follow-up, no conclusions on long term growth outcomes

can be reached.

Summary – Pediatric

Studies CL201 and CL205 enrolled children (5-12 y/o and 1-4 y/o respectively) with XLH, hypophosphatemia and rickets, and in most cases also leg bowing and growth delay. Both studies showed consistent, robust increases in serum phosphorus, and improvement in radiographic rickets scores and serum ALP, with no evidence of loss of these effects over time. The lack of a control group is a significant limitation, but comparison data from study CL002 support the conclusions. The applicant's proposed pediatric dosing scheme (starting dose 0.8 mg/kg Q2W with titration up to 2.0 mg/kg based on serum phosphorus) is supported by the data in the younger and older children.

There was little effect shown on growth and skeletal deformities, which require longer follow-up. Because of the central role of rickets in the pathogenesis of bone disease in XLH, children are expected to derive clinically meaningful benefits from treatment, especially when treatment is begun at a very young age. These studies did not include bone biopsies, which have previously shown improved osteomalacia with conventional therapy in pediatric patients. However, osteomalacia is essentially the same disorder in children as in adults, and the evidence of improvements in osteomalacia in the adult studies (see below) can reasonably be extrapolated to children and to adolescents through modeling.

Adult XLH

Compared to children, the goals of XLH treatment are less well defined, and the benefits of conventional therapy are not well established. Therefore, DBRUP required a placebo-controlled study in the adult XLH population (study CL303). Bone biopsy investigation of osteomalacia was also strongly recommended; this is being conducted in a separate, smaller study (CL304).

Study CL303

This is an ongoing randomized, double-blind, placebo-controlled phase 3 study. The primary objective is to demonstrate the effect, relative to placebo, on increasing serum phosphorus in this population; secondary objectives are to demonstrate effects on skeletal pain, stiffness and physical functioning. The enrollment criteria included age 18-65 y/o; XLH diagnosis with classic clinical features and *PHEX* mutation in patient or family member, or serum FGF23 > 30 pg/mL; serum phosphorus <2.5 mg/dL and TmP/GFR <2.5 mg/dL; skeletal pain with a score of ≥4 on the BPI-question 3 (worst pain in 24 hours); and eGFR ≥60 mL/min, or 45-60 mL/min with no evidence of nephrocalcinosis. Patients were randomized 1:1 to receive burosumab 1.0 mg/kg (maximum 90 mg) or matching placebo Q4W for 24 weeks, followed by open label burosumab at the same dose for all patients. As in other studies, concomitant phosphate or active vitamin D are not permitted; vitamin D is allowed for levels <20 ng/mL.

A total of 134 patients enrolled in study CL303 (68 burosumab/ 66 placebo); 51% of the patients enrolled at one of 8 sites in the U.S.; 35% enrolled at European and 13% at Asian sites. One

patient discontinued near the end of the 24-week double blind period; the remaining patients completed week 48. The mean age of enrollees was 40 years (range 18-66); 65% are female; 81% are white, 16% Asian and 3% other race; 91% are non-Hispanic. Most patients had received conventional therapy for many years, both as children and as adults, yet majorities had short stature, leg bowing, osteoarthritis, enthesopathy and (per protocol) significant bone or joint pain.

The primary endpoint, mean serum phosphorus >2.5 mg/dL (the LLN) at the midpoints of the 4-week dosing intervals between baseline and week 24, was achieved by 8% of placebo patients and 94% of burosumab patients ($p<0.0001$). The means at these midpoints were 2.08 and 3.24 mg/dL in the placebo and burosumab groups, which were increased from 1.92 and 2.03 mg/dL at baseline. Mean trough (pre-dose) level in the burosumab group was 2.72 mg/dL; therefore, serum phosphorus remained in normal range continuously for most burosumab treated patients. TmP/GFR showed similar increases from baseline in the burosumab group. Efficacy for the primary endpoint was consistent across subgroups of age (>50 , ≤ 50 years), sex, race and geographic region.

To measure clinical benefits in adults, the applicant chose three PROs as key secondary endpoints. XLH-related skeletal pain was measured by the BPI question 3, whereby the patient scored (on a 0-10 scale) their worst pain during the previous 24 hours, daily for 7 days prior to certain visits. In the placebo group, mean BPI-Q3 score declined from 6.54 at baseline to 6.09 at week 24. In the burosumab group, mean score declined from 6.81 at baseline to 5.82 at week 24. The LS mean difference was -0.46 (95% CI -1.00, 0.08; $p=0.09$). The lack of a clear benefit in pain reduction with burosumab is consistent with the complex nature of XLH-related pain in adults, which may result from many factors including osteoarthritis, enthesopathy and pseudofractures related to osteomalacia.

In the same diaries with the BPI questions, patients recorded daily pain medication use, although this was not a prespecified endpoint. At baseline, 68% of patients were using pain medications, including 22% who were using opioids. In both treatment groups, these percentages showed little change at weeks 12 or 24.

The other two key secondary PRO endpoints were based on the WOMAC questionnaire. Two WOMAC domains, Stiffness and Physical Function, were chosen to capture most of the musculoskeletal symptoms of adult XLH, and the data showed improving trends from baseline to week 24 in the burosumab group. However, the WOMAC was designed for patients with osteoarthritis, and COA reviewers concluded that it is not fit-for-purpose for the burosumab program, and not suitable for labeling.

A skeletal survey was conducted at baseline to identify osteomalacia-related abnormalities. Osteomalacia-related fractures were defined as atraumatic lucencies extending across both bone cortices and pseudofractures were defined as atraumatic lucencies extending across one

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cortex. There were 52% of patients who had either active (i.e., unhealed) fractures (12%) or active pseudofractures (47%) at baseline; almost all were located in the femurs, tibia/fibula, or metatarsals. Re-assessment of these sites at week 24 demonstrated higher rates of complete healing in the burosumab group compared to placebo for active fractures (50% versus 0%); active pseudofractures (41% versus 9%), and both combined (43% versus 8%). Readers of all images were blinded to treatment.

There was no evidence in this study of a loss of burosumab effects over time. Serum phosphorus increased maximally after the first one or two doses followed by a small decline, however mean peak and trough levels were then stable from week 12-48, remaining about 1.0 mg and 0.5 mg above baseline at peak and trough, respectively.

Study CL304

The primary efficacy objective of this ongoing study is to establish the effect of burosumab on XLH-associated osteomalacia, defined by bone biopsy-derived histomorphometry parameters, in adult patients. The enrollment criteria were essentially identical to study CL303, except that patients who had used oral phosphate and/or active vitamin D within 2 years were not eligible, in order to avoid any confounding effects of this therapy on biopsy findings. All patients receive open label burosumab 1.0 mg/kg Q4W (max. 90 mg), the same regimen as study CL303. Double labeled iliac crest bone biopsies are performed at baseline and week 48.

The study enrolled a total of 14 patients, who are similar demographically to the study CL303 population. Although the full study report is not yet available, histomorphometry data were submitted for the 11 patients with evaluable biopsies. Each of these 11 patients exhibited osteomalacia at baseline, with excess accumulation of unmineralized osteoid, and significant improvement at week 48. Mean osteoid volume as a proportion of bone volume (OV/BV, the primary endpoint) declined from 26.1% to 11.2% (-57% from baseline). Mean osteoid thickness (O.Th) declined from 17.2 μm to 11.6 μm (-33%). Mean osteoid surface (OS/BS) declined from 91.7% to 67.8% (-26%). Mineralization lag time (MLt) was not evaluable at baseline for 5 of the patients but was measureable in 10/11 at week 48. In the 6 paired specimens, mean MLt declined from 594 days to 156 days, a change of -74%.

Summary – Adult

Studies CL303 and CL304 enrolled adults with XLH, hypophosphatemia and significant pain at baseline. As in the pediatric studies, there were substantial increases from baseline serum phosphorus, with most patients achieving and maintaining levels in the normal range. The applicant's proposed adult burosumab dose of 1.0 mg/kg Q4W is well supported by these data. Compared to children with XLH, clinical benefits are harder to establish in the adult XLH population. Small declines in pain scores relative to placebo did not reach statistical significance, probably because the origins of pain in this population are complex, and pain related to factors such as osteoarthritis and deformities cannot be expected to respond to this drug. Alternatively, it is possible that responses to pain may require longer duration of

treatment and this would need to be evaluated with longer term data.

These studies also provided objective evidence of substantial reduction in osteomalacia, both indirect (radiographic pseudofractures or fractures) and direct (bone biopsy parameters). Although the clinical significance of these measures is uncertain, it is reasonable to assume that patients would benefit from this improvement in bone health.

8.3. Review of Safety

8.3.1. Safety Review Approach

In pediatric and adult XLH patients, ectopic mineralization was expected to be the predominant safety issue for burosumab, based on nonclinical studies in which elevated serum phosphorus (>8 mg/dL) was associated with mineralization in the kidney and other organs. This was considered to be caused by exaggeration of the pharmacologic suppression of FGF23. Thus, clinical studies included extensive monitoring of serum phosphorus and other relevant biochemical parameters including serum and urine calcium, and renal ultrasound and echocardiography to detect calcifications. Healthy subjects have not been exposed to burosumab in any study because it is believed that they would be, compared to XLH patients, at higher risk for ectopic mineralization. (For this reason, an IND clinical hold was briefly in effect in 2008, as noted in section 3.2 above.)

Other adverse events of interest that were prespecified in pivotal studies were injection site reactions, hypersensitivity, restless legs syndrome (because of multiple reports in the adult phase 2 studies), and immunogenicity.

Some of the safety data were pooled for all pediatric studies or for all adult studies, as appropriate, in the ISS and in this review. However, the potential safety concerns of burosumab are similar across different age groups.

8.3.2. Review of the Safety Database

Overall Exposure

A total of 65 children and 175 adults with XLH have received ≥ 1 dose of burosumab in 7 repeat-dose studies:

Pediatric XLH:

- Study CL201: age 5-12 years, N=52
- Study CL205: age 1-4 years, N=13

Adult XLH:

- Study CL303: N=134 (burosumab 68; placebo 66)
- Study CL304: N=14
- Study INT-001: N=28
- Study INT-002: N=22
- Study CL203: N=20

These studies were open label, in which all patients received burosumab, with the exception of CL303, in which half the patients received blinded placebo for the initial 24 weeks, before crossing over to burosumab.

Table 80 Burosumab safety population

Safety Database for Burosumab Individuals exposed to >1 dose of burosumab in this development program for XLH N=241*		
Clinical Trial Groups	Burosumab (n=241*)	Placebo (n=66)
Healthy volunteers	0	0
Phase 1 single dose (adults w/XLH)	47	9
Uncontrolled trials for pediatric XLH	65	-
Controlled trials for adult XLH*	134	66
Uncontrolled trials for adult XLH	42	-

*Patients assigned to placebo in study CL303 (n=66) crossed over to burosumab at week 24, and are counted only once for overall total of 241.
 Patients in phase 1 studies who received only 1 dose are also not counted in overall total.
 One adult patient enrolled in study INT-001 and later enrolled in study CL303; because there was a >4 year gap in between, the patient was counted twice in total repeat-dose N=241 and adult repeat-dose 176, but the numbers of unique patients was one less (N=240 and 175 respectively).

The longest duration of continuous burosumab exposure has been in pediatric patients age 5-12 years old: As of the cutoff date for the 120-Day Safety Update, mean exposure duration in study CL201 was 123.5 weeks. In study CL205 (1-4 year olds), mean exposure was 45 weeks. In the adult phase 2 studies, mean exposure in studies INT-001/002 (N=28) was 50 weeks, and for those subjects who subsequently enrolled in study CL203 (after a treatment gap of 1.5-3.5 years, N=20), mean exposure in CL203 was 106.7 weeks (per 120-day safety update). In the adult phase 3 studies (CL303 and CL304), mean exposure was 48.1 and 51.2 weeks, respectively.

Table 81 Burosumab duration of exposure, by age group

Dosage	Number of patients exposed to the study drug:				
	>= 1 day to <12 weeks	>=12 weeks to <24 weeks	>=24 weeks to <48 weeks	>=48 weeks to <72 weeks	>= 72 weeks
Age 1-4 years	N=0	N=0	N=11	N=2	N=0
Age 5-12 years	N=0	N=0	N=0	N=0	N=52
Adults	N=0	N=5	N=65	N=75	N=31
Safety Update cutoffs: 5/18/17 (CL201); 4/20/17 (CL205); 6/8/17 (CL303, CL304, CL203)					
Source: ISS Safety Update Tables 14.1.1.4.1 and 14.2.1.4.1					

In earlier studies (INT-001/002, CL203, CL201), doses were titrated to an effective dose based on maintaining serum phosphorus in the normal range, and later studies (CL205, CL303, CL304) used the doses selected for labeling. Thus, essentially all exposed patients received effective doses of burosumab. Overall, the average dose per 4 week period in pediatric patients was 1.53 mg/kg (1.62 mg/kg in patients dosed Q2W) and in adult patients was 0.92 mg/kg.

Relevant characteristics of the safety population:

Baseline characteristics of the pooled pediatric population (5-12 year olds in study CL201 and 1-4 year olds in study CL205) are presented in the table below. The mean age for the overall pediatric population was 7.4 years. The overall sex distribution was equal although there was a predominance of boys in the younger group (9/13 patients in CL205). Most patients were in the U.S. (75%) and most were white (89%) and non-Hispanic (94%). Patients were generally short for age with a mean height z-score of -1.8 and mean height percentile of 10.5%. Mean serum phosphorus level was 2.4 mg/dL.

Table 82 Demographic and baseline characteristics in pediatric studies

	Study CL201 N=52	Study CL205 N=13	Total N=65
Age (years), mean (SD)	8.5 (1.9)	2.9 (1.2)	7.4 (2.8)
Sex – n(%)			
Male	24 (46)	9 (69)	33 (51)
Female	28 (54)	4 (31)	32 (49)
Race – n(%)			
White	46 (88)	12 (92)	58 (89)
Black or African American	2 (4)	1 (8)	3 (5)
Other	4 (8)	0	4 (6)
Ethnicity – n (%)			
Hispanic	2 (4)	2 (15)	4 (6)
Non-Hispanic	50 (96)	11 (85)	61 (94)
Country – n (%)			
U.S.	36 (69)	13 (100)	49 (75)
U.K.	10 (19)	0	10 (15)
Netherlands	4 (8)	0	4 (6)
France	2 (4)	0	2 (3)
BMI (kg/m ²), mean	20.3	16.3	19.5
Height Z-score, mean (SD)	-1.9 (1.0)	-1.4 (1.2)	-1.8 (1.0)
Total RSS, mean	1.80	2.92	2.02
Serum phosphorus (mg/dL), mean	2.33	2.51	2.36

Source: ISS Table 14.1.1.2.1

Baseline demographics for the pooled adult study populations is presented in the table below. The average age at enrollment was about 40 years (in study CL203, average age at enrollment was 46 years, i.e. about 4 years older than these patients' average age at their previous enrollment in study INT-001). Only 2 patients were older than 65 years; therefore, the applicant analyzed subgroups of ≤50 and >50 years. About 2/3 of patients were female, consistent with X-linked dominant inheritance. Most patients were white (82%) and non-Hispanic (91%). In study CL303, patients were enrolled at sites in the U.S. (51%), Europe/UK (35%) and Japan/S. Korea (13%). In studies INT-001/INT-002/CL203, 27/28 patients were enrolled in the U.S. and the other patient in Canada.

Table 83 Demographic and baseline characteristics in adult studies

	Study CL303 N=134	Study CL304 N=14	Studies INT-001/002 N=28	Overall N=176
Age (years)				
Mean (SD)	40.0 (12.2)	40.1 (8.7)	41.9 (13.8)	40.3 (12.2)
Age ≥18 to ≤50, n (%)	106 (79)	12 (86)	17 (61)	135 (77)
Age >50, n (%)	28 (21)	2 (14)	11 (39)	41 (23)
Sex – n (%)				
Male	47 (35)	6 (43)	9 (32)	62 (35)
Female	87 (65)	8 (57)	19 (68)	114 (65)
Race – n (%)				
White	108 (81)	9 (64)	27 (96)	144 (82)
Black or African American	3 (2)	1 (7)	1 (4)	5 (3)
Asian	21 (16)	4 (29)	0	25 (14)
Other	2 (1)	0	0	2 (1)
Ethnicity – n (%)				
Hispanic	12 (9)	1 (7)	2 (7)	15 (9)
Non-Hispanic	122 (91)	13 (93)	25 (89)	160 (91)
Not reported	0	0	1 (4)	1 (<1)
BMI (kg/m ²), mean	30.3	30.8	34.2	31.0
Serum phosphorus, mean (mg/dL)	1.98	2.30	1.89	2.00
Source: ISS Table 14.2.1.2.1				

Adequacy of the safety database

In total, 236 patients with XLH have received burosumab for ≥6 months. This is below the ICH standard of ~300-600 patients exposed to a new drug for ≥6 months, but adequate given the relative rarity of XLH. Most of the subjects have been enrolled at US sites and demographics likely correspond well to the US target population. The main limitation of the safety database is the lack of a control group for safety data in the pediatric population. There also are uncertainties about long-term safety (primarily, nephrocalcinosis and renal function, and spinal stenosis) and about safety of use during pregnancy and lactation, which should be addressed in PMRs (see section 10).

8.3.3. Adequacy of Applicant’s Clinical Safety Assessment

Issues Regarding Data Integrity and Submission Quality

There were no important issues regarding safety data quality or integrity that were apparent during the review. In studies CL201 and CL303, the number of AEs reported per patient was very high across all study sites. The quality of the submission was generally high and did not present major difficulties with respect to conducting the safety review.

Categorization of Adverse Events

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of either the investigator or Ultragenyx, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

AEs were also classified for severity using the NCI CTCAE v. 4.0 whenever possible, and when not possible by investigators, based on definitions in the protocol:

- Mild (Grade 1): awareness of sign or symptom, but easily tolerated
- Moderate (Grade 2): discomfort enough to cause interference with normal daily activities
- Severe (Grade 3): inability to perform normal daily activities
- Life-threatening (Grade 4): place the participant at immediate risk of death or are disabling
- Death (Grade 5): events that result in death

AEs were classified by MedDRA version 18.1 and were grouped for analysis by SOC and PT. Both patient incidence and rate (number of events per patient-year) were presented. Prespecified events to monitor were as follows:

- Injection site reactions: Defined by the HLT Injection site reaction
- Hypersensitivity: Defined by PTs in the narrow SMQs “hypersensitivity”, “severe cutaneous adverse reactions”, “anaphylactic reaction”, and “angioedema”
- Hyperphosphatemia: PTs of hyperphosphatemia, blood phosphorus increased and blood phosphorus abnormal
- Ectopic mineralization: Defined by PTs related to ectopic calcification, listed in the SAP
- Restless legs syndrome: Defined by the PTs restless legs syndrome, restlessness, akathisia, psychomotor hyperactivity, sensory disturbance, muscle cramp, limb discomfort, neuromuscular pain and formication

Reviewer Comments:

The applicant’s methods of collection, categorization and analysis of adverse events, including translation of verbatim terms to preferred terms and “lumping” of certain types of AEs were appropriate.

Routine Clinical Tests

Multiple clinical laboratory tests were monitored as safety parameters frequently throughout all studies, especially those related to XLH and the mechanism of action of burosumab, i.e.

serum calcium, phosphorus, creatinine and iPTH as well as urine calcium and creatinine. Central labs were used in the pivotal studies. Designation of an abnormal lab finding as an AE was at the discretion of investigators.

For detection of potential ectopic calcification, renal ultrasound was included in all studies and echocardiogram was conducted in the pivotal studies except for CL205 (because of their very young age). The potential for LVH based on excess FGF23 was investigated by ECGs and echocardiograms.

Reviewer Comments:

These assessments were adequate.

8.3.4. Safety Results

Deaths

There were no deaths in any of the XLH studies, pediatric or adult, through the data cutoffs for the 120-day safety update. After the cutoff date for study CL303, patient # (b) (6), a 41-year-old male, died in an auto accident caused by another driver while driving home from work.

In a phase 2 study of burosumab in the treatment of tumor-induced osteomalacia (TIO), a 59-year-old man with Pickwickian syndrome and a history of radical surgery for bladder cancer died from septic shock following an ERCP for gallstone pancreatitis and other complications.

Serious Adverse Events

Pediatric Serious Adverse Events

Among the 65 pediatric patients in the phase 2 studies, there were 2 with reported SAEs:

- In study CL201, patient # (b) (6), an 8-year-old girl, experienced SAEs of **pyrexia** and **myalgia**. On study day 336, she experienced muscle pain in both thighs and legs following a burosumab injection earlier in the day. The following day she developed a fever of 38.9°C and was hospitalized. Evaluation was unremarkable except for eosinophilia of 14.2%. The symptoms resolved and she was discharged the next day, and eosinophilia resolved. A rheumatologist attributed the lower limb pain to XLH, and she is continuing on treatment without recurrence. The patient's mother stated that similar symptoms of musculoskeletal pain and fever had previously occurred on study day 30, two days after the second burosumab injection. The investigator considered the events possibly related to burosumab (narrative summary and CRF in original BLA).
- In study CL205, patient # (b) (6), a 4-year-old boy with a history of tooth abscess experienced fever and facial swelling at week 35 of burosumab treatment. The patient was admitted to the hospital for antibiotic treatment and surgical drainage of a **tooth abscess**; the event resolved within 3 days and the patient continues on burosumab. The

event was considered unlikely related to burosumab (narrative summary in 120-day safety update).

Also in the ongoing pediatric XLH phase 3 study CL301 (enrollment = 61), two patients have reported SAEs: a 5-year-old boy in the active-control arm (phosphate/calcitriol arm) with **hematuria**, and a 10-year-old boy (burosumab arm) with **migraine**, with symptoms of R arm and facial numbness lasting 10 minutes, with headache and vomiting. These SAEs resolved and both patients continue in the study (narratives in 120-day update; no other data yet available from this study).

Adult Serious Adverse Events

Among the 176 adult XLH patients, there were 28 patients (16%) with a total of 31 SAEs in all studies through the cutoff for the 120-Day Safety Update, including 2 patients in each of the study CL303 double-blind groups (i.e. through week 24).

Table 84 Serious AEs in adult studies, by SOC/PT (SAS)

System Organ Class Preferred Term Subject incidence: n (%)	Study CL303		Total Buros* (N=134)	Study CL304 N=14	Study CL203 N=20	Studies INT- 001/002 N=28	Overall Buros N=176
	Double blind (wk 0-24)						
	Placebo (N=66)	Buros (N=68)					
Patients with serious TEAEs, n(%)	2 (3)	2 (3)	15 (11)	2 (14)	9 (45)	3 (11)	28 (16)
Number of serious TEAEs	2	2	17	2	9	3	31
Musculoskeletal and connective tissue disorders	0	1 (1.5)	7 (5)	0	2 (10)	1 (4)	10 (6)
Cervical spinal stenosis	0	0	1	0	0	1	2
Arthralgia	0	0	1	0	0	0	1
Back pain	0	1	1	0	0	0	1
Joint range of motion decreased	0	0	1	0	0	0	1
Musculoskeletal chest pain	0	0	0	0	1	0	1
Musculoskeletal pain	0	0	1	0	0	0	1
Osteoarthritis	0	0	0	0	1	0-	1
Pseudarthrosis	0	0	1	0	0	0	1
Spinal column stenosis	0	0	1	0	0	0	1
Gastrointestinal disorders	0	1 (1.5)	3 (2)	0	1 (5)	0	4 (2)
Colitis	0	0	1	0	0	0	1
Irritable bowel syndrome	0	1	1	0	0	0	1
Periodontal disease	0	0	1	0	0	0	1
Small intestinal obstruction	0	0	0	0	1	0	1
Neoplasms benign, malignant and unspec. (incl cysts and polyps)	1 (1.5)	0	0	0	3 (15)	1 (4)	4 (2)
Adenocarcinoma of colon	0	0	0	0	1	0	1
Breast cancer	0	0	0	0	0	1	1

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System Organ Class Preferred Term Subject incidence: n (%)	Study CL303		Total Buros* (N=134)	Study CL304 N=14	Study CL203 N=20	Studies INT- 001/002 N=28	Overall Buros N=176
	Double blind (wk 0-24)						
	Placebo (N=66)	Buros (N=68)					
Chordoma	0	0	0	0	1	0	1
Lung adenocarcinoma	0	0	0	0	1	0	1
Invasive ductal breast carcinoma	1	0	0	0	0	0	0
Nervous system disorders	0	0	2 (1.5)	2 (15)	0	0	4 (2)
Migraine	0	0	0	1	0	0	1
Myelopathy	0	0	1	0	0	0	1
Paresthesia	0	0	0	1	0	0	1
Presyncope	0	0	1	0	0	0	1
Hepatobiliary disorders	0	0	1 (0.7)	0	1 (5)	0	2 (1)
Cholecystitis acute	0	0	0	0	1	0	1
Cholelithiasis	0	0	1	0	0	0	1
Injury, poisoning and procedural complications	0	0	2 (1.5)	0	0	0	2 (1)
Procedural nausea	0	0	1	0	0	0	1
Procedural vomiting	0	0	1	0	0	0	1
Subdural hematoma	0	0	1	0	0	0	1
Cardiac disorders	0	0	1 (0.7)	0	0	0	1 (0.6)
Palpitations	0	0	1	0	0	0	1
Infections and infestations	1 (1.5)	0	0	0	1 (5)	0	1 (0.6)
Medical device site joint infection	0	0	0	0	1	0	1
Upper respiratory tract infection	1	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	1 (5)	0	1 (0.6)
Angioedema	0	0	0	0	1	0	1
Vascular disorders	0	0	0	0	0	1 (4)	1 (0.6)
Hypertensive crisis	0	0	0	0	0	1	1

*All patients who received burosumab in study CL303; length of burosumab treatment varies as it includes both patients randomized to burosumab, and patients randomized to placebo who crossed over to burosumab at week 24
 Data as of 120 day safety update cutoff of 6/8/17 for ongoing studies (CL303, CL304, CL203)
 Source: ISS Safety Update Table 14.2.3.1.1 and Table 14.2.3.1.10

Events listed in the above table were reported by the Safety Update cutoff date for adult studies (6/8/17). Subsequently, through 9/30/17, SAEs were reported in 8 additional patients: in study CL303, SAEs of stress fracture, gastroenteritis, road traffic accident, focal dyscognitive seizures, spondylolisthesis, duodenal ulcer and parathyroid tumor benign; and in study CL203, SAEs of hemianesthesia and hemiparesis in 1 patient. Narratives of all SAEs through 9/30/17 are included in either the original BLA (M2.7.4.2.2) or the 120-day update (section 10.2); CRFs for SAEs reported in the original BLA are included in the study reports.

Among all these SAEs, none resulted in study or treatment discontinuation. One event (**angioedema**) was considered possibly treatment related. In study CL203, patient # (b) (6), a

68-year-old woman with hypertension on multiple medications (including lisinopril) experienced throat tightening, swollen face and tongue on day 392 of burosumab, occurring about 15 hours after an injection. At an ER she was diagnosed with angioedema and symptoms resolved after treatment with diphenhydramine and epinephrine. The ER staff suspected that lisinopril was the cause and this drug was discontinued. The patient is continuing burosumab without any recurrence. The investigator assessed the SAE as CTCAE Grade 4 (life-threatening) and possibly related to burosumab, and also possibly related to lisinopril.

There was one patient with an SAE related to fracture:

- In study CL303, patient #1 (b) (6), a 40-year-old female with numerous active pseudofractures present on the baseline skeletal survey including the R femoral mid shaft, was randomized to the burosumab arm. After 17 months she had increasing pain in her R femur and underwent surgery for **stress fracture** of R femur with the aim “to correct bowing deformity.....and improve the biomechanics of her ambulation”. The event was assessed as not related to burosumab.

As noted above, no SAE occurred in ≥ 1 patient except for cervical spinal stenosis, reported in the following 2 patients:

- In study INT-001/002, patient # (b) (6), a 34-year-old male had a longstanding history of low back pain that worsened while receiving burosumab in the study. An MRI on day 103 showed **cervical spinal stenosis**. On day 310, a C-3 to C-6 posterior fusion was performed. The patient reported persistent back pain at the final study visit on day 347.
- In study CL303, patient # (b) (6), a 45-year-old female with a history of peripheral neuropathy, experienced bilateral paresthesias in hands and arms ~3 months after enrollment (while receiving blinded placebo), and **cervical spinal stenosis** was diagnosed by CT and MRI on days 113 and 143. After crossing over to burosumab at day 168, she underwent laminectomy on day 240. The spinal stenosis was attributed to underlying XLH.

The 120-day update reported 4 additional patients who underwent spinal surgery during study CL303 (open label phase) or CL304:

- Patient # (b) (6), a 43-year-old female with a long history of back problems including spinal stenosis, multilevel foraminal stenosis, sacroiliac pain and degenerative disk disease, was noted on baseline study xrays to have anterior **spondylolisthesis**. She was randomized to burosumab in study CL303. On study day 384, she underwent L5-S1 fusion. The investigator assessed the spondylolisthesis as unrelated to study drug.
- Patient # (b) (6), a 42-year-old female was observed at screening to have “diminished cervical range of motion”. She was randomized to placebo in study CL303. On study day 350, she underwent C2 to C7 laminectomy for decompression of cervical spinal cord. The SAE was identified as **joint range of motion decreased**. The investigator considered the event not related to study drug.

- Patient # (b) (6), a 47-year-old female had a past history of multilevel spinal stenosis with prior laminectomies (C2-C6 in 2003; C6-T3 and L3-L5) and ossification of the posterior longitudinal ligament. She was randomized to burosumab in study CL303. On study day 170, during the 6MWT she noticed leg weakness. On day 218 an MRI found multilevel neural foraminal narrowing and multilevel spinal stenosis, which was most severe at T10-11 and T11-12, with T2 hyperintensity within the cord at T10-11, indicative of active myelopathy. On day 220, she was admitted for progressive difficulty with ambulation, and underwent a T10-11 laminectomy. Subsequently, she underwent PT/OT and regained some mobility, but the events had not resolved as of study day 486. There were 2 SAEs designated as **spinal column stenosis** and **myelopathy**, considered unlikely related to study drug and related to the patient's pre-existing multilevel spinal stenosis related to XLH.
- In study CL304, patient # (b) (6), a 39-year-old male with a history of thoracic decompression surgery for lower leg weakness, spinal stenosis and spasticity, reported increasing frequency of lower extremity numbness and spasm over 4.5 months prior to screening. The symptoms of paresthesia worsened after study day 171, and he underwent thoracic spine surgery on day 215; the symptoms resolved. The SAE was designated as **paresthesia** and attributed by the investigator to his known thoracic compression syndrome rather than study drug.

Reviewer Comments:

These cases represent a high incidence of spinal surgery (laminectomy or fusion) in 6/176 (3.4%) patients in the adult XLH studies. In response to an IR, the applicant provided additional information (SD-42, 2/5/18). In each of the 6 cases it appears that the underlying condition involved spinal stenosis which was present before burosumab treatment. In 4 of the patients (# (b) (6)), the symptoms were reported to have worsened during the study. However, for patient # (b) (6), symptom worsening occurred during initial treatment with placebo, and patients # (b) (6) and # (b) (6) had had previous laminectomies. In the 2 remaining patients (# (b) (6)), there was no reported change in symptoms during the study and it appears that surgery may have been considered or planned prior to treatment.

Although unlikely, it cannot be ruled out that burosumab may exacerbate spinal stenosis, if for example it were to worsen enthesopathy (calcification) of spinal ligaments. Spinal stenosis is highly prevalent in XLH (reported in medical history by 19% of study CL303 patients) and cord compression has been described in at least 26 case reports in literature. The most frequently cited causes in these reports have been thickening of the laminae, ossification of ligaments (posterior longitudinal ligament, ligamentum flavum) and facet hypertrophy. Narrowing of the spinal canal in XLH, possibly developmental, has also been reported. Radiographic findings in the 6 current patients were varied and generally similar to those reported in the literature. It should also be noted that in 4 literature articles (total of 9 adults with XLH), neurologic deterioration occurred within a few months to 2 years after initiation of vitamin D in high doses

or active vitamin D. Although most reported cases of spinal cord compression in XLH have occurred in untreated patients, some authors have speculated that vitamin D may exacerbate an existing stenosis (Highman et al, Q J Med 1970, 39:529; Bussiere et al, Rev Rhum Ed Fr 1993, 60:64). Based on the somewhat similar mechanism of burosumab and the 6 cases reported, spinal stenosis warrants continued monitoring as a potential safety issue in a PMR study.

Upon review of the SAE narratives other than these 6 cases of spinal stenosis/surgery, I agree with the Investigator/ applicant assessments that none of the events appear to be directly related to burosumab treatment. Overall, the incidence of SAEs among these adults with XLH is 20% to date, which is high for a population with mean age of about 40 years old. However, many of these patients have considerable baseline XLH-related morbidity which contributed to many of these events.

Withdrawal and/or Discontinuations Due to Adverse Effects

None of the 65 pediatric patients (studies CL201 and 205) have discontinued due to an adverse event (or for any reason).

In the adult phase 2 studies (INT-001/002), 3 out of 28 patients discontinued burosumab due to the following adverse events:

- Patient # (b) (6), a 32-year-old WF with history of allergies and asthma, experienced **injection site urticaria** on day 57 following a burosumab injection
- Patient # (b) (6), a 54-year-old WM with a history of nephrocalcinosis and **nephrolithiasis**, experienced hematuria on day 4 of study INT-002 (3 days after 5th dose overall) and passed a kidney stone on day 15; ultrasound on day 58 showed nephrolithiasis and nephrocalcinosis
- Patient # (b) (6), a 39-year-old WF with history of **restless legs syndrome (RLS)**, experienced increased RLS symptoms 2 weeks after the last injection in study INT-001 and a severe worsening with R arm involvement on day 135 of study INT-002; symptoms returned to baseline by 6 weeks after discontinuation of burosumab

Each of these 3 patients subsequently enrolled in study CL203; patient # (b) (6) had another episode of nephrolithiasis 42 weeks into that study.

There have been no discontinuations due to a TEAE in studies CL203, CL303, or CL304.

Significant Adverse Events

Including the 120-day safety update, there were 3 pediatric patients who experienced TEAEs that were Grade 3 in severity (none were Grade 4): An event of tooth abscess; an event of rash, which was reported as resulting from swimming in a lake; and an event of food allergy (allergic reaction to raw egg). Each event was considered by the investigator to be not related to study treatment.

In the double blind phase of study CL303, grade 3 TEAEs were reported for 8 (12%) subjects in the burosumab group and 9 (14%) subjects in the placebo group; no Grade 4 TEAEs were reported. Across all adult studies (N=176), 23 patients (13%) had severe (Grade 3 or 4) AEs during burosumab treatment; one (the SAE of angioedema discussed above) was Grade 4.

In regard to the potential for ADCC with type II hypersensitivity (see nonclinical review section), there were no reports of autoimmune diseases of the type commonly associated with type II cytotoxic reactions, e.g. Graves disease, autoimmune hemolytic anemia or thrombocytopenia. In theory, ADCC reactions with burosumab in XLH may involve tissues with high concentration of α -klotho, especially proximal and distal renal tubules, parathyroid, choroid plexus or cardiovascular tissues. There were no reports of hypoparathyroidism in clinical studies.

Among all studies, 5 patients had AEs of clinical fracture reported:

- Study CL201, patient # (b) (6) (12 years old M): Fractured finger on day 575
- Study CL203, patient # (b) (6) (56 years old F): Fractured thumb on day 11
- Study CL203, patient # (b) (6) (62 years old M): Femoral neck fracture on day 253
- Study CL303: patient # (b) (6) (46 years old F): Stress fracture of foot, day 47 of placebo
- Study CL303: patient # (b) (6) (61 years old M): Metatarsal fracture, day 167 of burosumab

Treatment Emergent Adverse Events and Adverse Reactions

Pediatric Treatment Emergent Adverse Events

All pediatric patients experienced at least one TEAE. The following table lists all TEAE terms that were reported in at least 20% of patients in studies CL201 and CL205 as of the Safety Update data cutoffs, representing 123 and 45 weeks of treatment, respectively. The incidence of most TEAEs was similar between the Q4W and Q2W dose groups in study CL201; incidence was generally somewhat lower in study CL205, possibly related to the shorter follow-up time. Injection site reactions (ISRs) were the most frequent category of AEs, and are discussed further in section 8.3.5. The majority of other events were either routine minor pediatric conditions (URI, nasopharyngitis, cough, etc.), or were symptoms common in XLH (e.g. pain in extremity, arthralgia). Events of particular interest (ISRs, ectopic mineralization, renal function, hyperphosphatemia, hypersensitivity) are discussed further in section 10.5.

Table 85 Pediatric XLH studies: TEAEs reported in ≥20% of patients, by SOC/PT (SAS)

System Organ Class Preferred term Subject incidence: n (%)	Study CL201			Study CL205	Overall N=65
	Q4W* N=26	Q2W N=26	Total N=52	Q2W N=13	
Patients with any TEAE, n (%)	26 (100)	26 (100)	52 (100)	13 (100)	65 (100)
Infections and infestations					
Upper respiratory tract infection	12 (46)	11 (42)	23 (44)	7 (54)	30 (46)
Nasopharyngitis	14 (54)	13 (50)	27 (52)	2 (15)	29 (45)
Respiratory, thoracic and mediastinal disorders					
Cough	13 (50)	19 (73)	32 (62)	10 (77)	42 (65)
Rhinorrhea	10 (39)	10 (39)	20 (39)	5 (39)	25 (39)
Oropharyngeal pain	10 (39)	11 (42)	21 (40)	1 (8)	22 (34)
Nasal congestion	9 (35)	9 (35)	18 (35)	3 (23)	21 (32)
Gastrointestinal disorders					
Vomiting	14 (54)	11 (42)	25 (48)	6 (46)	31 (48)
Diarrhea	10 (39)	6 (23)	16 (31)	4 (31)	20 (31)
Abdominal pain upper	7 (27)	10 (39)	17 (33)	2 (15)	19 (29)
Nausea	6 (23)	7 (27)	13 (25)	1 (8)	14 (22)
Toothache	6 (23)	6 (23)	12 (23)	2 (15)	14 (22)
General disorders and administration site conditions					
Pyrexia	12 (46)	11 (42)	23 (44)	8 (62)	31 (48)
Injection site reaction	12 (46)	11 (42)	23 (44)	1 (8)	24 (37)
Injection site erythema	8 (31)	13 (50)	21 (40)	1 (8)	22 (34)
Nervous system disorders					
Headache	18 (69)	20 (77)	38 (73)	1 (8)	39 (60)
Musculoskeletal and connective tissue disorders					
Pain in extremity	14 (54)	10 (39)	24 (46)	3 (23)	27 (42)
Arthralgia	14 (54)	8 (31)	22 (42)	3 (23)	25 (39)
Skin and subcutaneous tissue disorders					
Rash	6 (23)	7 (27)	13 (25)	1 (8)	14 (22)
Ear and labyrinth disorders					
Ear pain	7 (27)	8 (31)	15 (29)	2 (15)	17 (27)
Immune system disorders					
Seasonal allergy	9 (35)	5 (19)	14 (27)	0	14 (22)

* Patients randomized to Q4W, but switched to Q2W after week 64
 Data as of 5/18/17 and 4/20/17 cutoffs for CL201 and CL205 studies respectively (120-day safety update)
 Source: ISS Safety Update Table 14.1.3.1.5

Based on the data, the applicant selected the following AEs for listing in labeling section 6.1 ADVERSE REACTIONS as reported in >10% of pediatric patients:

- Injection site reaction (includes all PTs in HLT of ISR) (total n both studies = 38, or 59%)
- Headache (n=39, or 60%)
- Pain in extremity (n=27, or 42%)
- Vitamin D decreased (total of 3 PTs, n=21 or 32%)
- Rash (total of 4 PTs, n=15 or 23%)

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- Toothache (n=14, or 22%)
- Myalgia (n=10, or 15%)
- Tooth abscess (n=11, or 17%)
- Dizziness (total of 2 PTs, n=8 or 12%)

Reviewer Comments:

In the absence of a control or prospective comparator group, some of these data are difficult to interpret. There were several AEs that were reported in >10% of patients but are generally minor, common pediatric conditions (URI, cough, vomiting, rhinorrhea, pyrexia, abdominal pain, oropharyngeal pain, diarrhea, seasonal allergy, nausea, pharyngitis streptococcal, ear pain or infection) and with no signal in the placebo-controlled adult trial; therefore, were not selected for the table in section 6.1. I agree that none of these adverse events are of specific clinical concern with the exception of pyrexia, because of the high incidence (48%) and one reported SAE; and vomiting, for which there was no adult signal but for which the pediatric incidence (48%) was very high, and was higher than in previous pediatric studies of oral bisphosphonates, which unlike burosumab have established GI tolerability issues.

Among the AEs selected for the table in section 6.1, some were included in part because of higher-than-placebo incidence in adults (headache, dizziness, vitamin D decreased, toothache, tooth abscess); and others because of possible relation to XLH (pain in extremity and myalgia). Arthralgia was not included because of higher incidence with placebo in the adult study (see below). I agree with these determinations by the applicant and believe these events should be labeled.

Adult Treatment Emergent Adverse Events

The most relevant adverse event data in adults are from the initial 24-week double blind phase of study CL303, representing the only placebo-controlled data in the BLA. Including the 24-week open label phase of this study, mean total burosumab exposure in these 134 patients was about 48 weeks as of the 120-Day Safety update. Longer term data are available from phase 2 study CL203, with mean burosumab exposure of 106.7 weeks (these patients also had received burosumab for a mean of 50 weeks in studies INT-001/002, followed by a time delay of 1.5-3.5 years before enrollment in CL203).

In study CL303 up to week 24, TEAEs were reported by 92% of placebo and 94% of burosumab recipients. Table 86 below represents AEs for which incidence was $\geq 2\%$ in the double blind burosumab group of study CL303 and higher than placebo (two left columns); these include back pain (15%, 9%); tooth abscess (13%, 8%); headache (13%, 8%); restless legs syndrome (12%, 6%); and nasopharyngitis (13%, 9%). Conversely, there were more AEs in the placebo versus burosumab group for arthralgia (24%, 9%); pain in extremity (15%, 7%); and oropharyngeal pain (11%, 2%).

Longer-term burosumab exposure (open label) is represented by the 4 right columns of the

table. The most frequent TEAEs in this overall adult group (total N=176) were arthralgia (21%); nasopharyngitis (21%); back pain (18%); headache (15%); pain in extremity (12%); and fatigue (11%). The incidence of arthralgia increased from 9% in the burosumab double blind cohort to 24% in the total-burosumab cohort in study CL303, with exposure adjusted incidence increasing from 0.19 to 0.38 events per year; however, this may be due to unexpectedly low rate in double blind. There were no other frequent AEs with apparent increasing incidence over time.

Table 86 Adult XLH studies: TEAEs reported in ≥2% of burosumab patients and more frequent than placebo in double-blind phase of study CL303, by SOC/PT (SAS)

System Organ Class Preferred term Subject incidence: n (%)	Study CL303		Total Buros* (N=134)	Study CL304 N=14	Study CL203 N=20	Studies INT- 001/002 N=28
	Double blind (wk 0-24)					
	Placebo (N=66)	Buros (N=68)				
Patients with any TEAE, n(%)	61 (92)	64 (94)	131 (98)	14 (100)	20 (100)	27 (96)
Infections and infestations						
Nasopharyngitis	6 (9)	9 (13)	30 (22)	3 (21)	6 (30)	12 (43)
Tooth abscess	5 (8)	9 (13)	18 (13)	4 (29)	2 (10)	1 (4)
Pharyngitis	1 (1.5)	2 (3)	3 (2)	1 (7)	0	1 (4)
Musculoskeletal and connective tissue disorders						
Back pain	6 (9)	10 (15)	22 (16)	4 (29)	6 (30)	9 (32)
Muscle spasms	2 (3)	5 (7)	12 (9)	4 (29)	2 (10)	3 (11)
Myalgia	1 (1.5)	3 (4)	9 (7)	0	2 (10)	3 (11)
Nervous system disorders						
Headache	5 (8)	9 (13)	27 (20)	2 (14)	4 (20)	6 (21)
Restless legs syndrome	4 (6)	8 (12)	15 (11)	1 (7)	1 (5)	5 (18)
Dizziness	4 (6)	7 (10)	10 (8)	1 (7)	3 (15)	6 (21)
Lethargy	0	2 (3)	3 (2)	0	1 (5)	0
General disorders and administration site conditions						
Injection site erythema	2 (3)	3 (4)	8 (6)	0	2 (10)	2 (7)
Peripheral swelling	1 (1.5)	2 (3)	3 (2)	1 (7)	0	2 (7)
Gastrointestinal disorders						
Nausea	6 (9)	7 (10)	12 (9)	2 (14)	4 (20)	4 (14)
Toothache	1 (1.5)	3 (4)	15 (11)	1 (7)	0	2 (7)
Constipation	0	6 (9)	6 (5)	3 (21)	2 (10)	1 (4)
Injury, poisoning and procedural complications						
Procedural pain	0	4 (6)	11 (8)	5 (36)	1 (5)	3 (11)
Contusion	1 (1.5)	2 (3)	4 (3)	1 (7)	1 (5)	2 (7)
Road traffic accident	1 (1.5)	2 (3)	3 (2)	0	0	0
Investigations						
Blood PTH increased	1 (1.5)	4 (6)	7 (5)	0	0	0
Blood 25-OH-cholecalciferol decreased	0	2(3)	3 (2)	1 (7)	0	0

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System Organ Class Preferred term Subject incidence: n (%)	Study CL303		Total Buros* (N=134)	Study CL304 N=14	Study CL203 N=20	Studies INT- 001/002 N=28
	Double blind (wk 0-24)					
	Placebo (N=66)	Buros (N=68)				
Blood glucose increased	0	2 (3)	4 (3)	0	0	0
Blood phosphorus increased	0	3 (4)	3 (2)	0	0	0
Respiratory, thoracic and mediastinal disorders						
Rhinorrhea	3 (5)	4 (6)	6 (5)	0	1 (5)	0
Skin and subcutaneous disorders						
Alopecia	0	2 (3)	2 (2)	0	0	1 (4)
Metabolism and nutrition disorders						
Vitamin D deficiency	3 (5)	5 (7)	14 (10)	2 (14)	0	0
Psychiatric disorders						
Depression	1 (1.5)	2 (3)	9 (7)	0	3 (15)	2 (7)
Ear and labyrinth disorders						
Vertigo	1 (1.5)	2 (3)	3 (2)	0	2 (10)	3 (11)
Reproductive system and breast disorders						
Dysmenorrhea	0	2 (3)	2 (2)	1 (7)	1 (5)	2 (7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Melanocytic nevus	0	2 (3)	2 (2)	0	0	0
*All patients who received burosumab in study CL303; length of burosumab treatment varies as it includes both patients randomized to burosumab, and patients randomized to placebo who crossed over to burosumab at week 24 Data as of 120 day safety update cutoff of 6/8/17 for ongoing studies (CL303, CL304, CL203) Source: ISS Safety Update Table 14.2.3.1.5						

Based on these data, the applicant selected the following AEs for listing in labeling section 6.1 ADVERSE REACTIONS as reported in >5% of adult patients and ≥2 patients more than placebo in study CL303:

- Back pain
- Headache
- Tooth infection (includes tooth infection, tooth abscess)
- Restless legs syndrome
- Vitamin D decreased (includes vitamin D deficiency, blood 25-OH-cholecalciferol decreased, vitamin D decreased)
- Dizziness
- Constipation
- Blood phosphorus increased (includes hyperphosphatemia, blood phosphorus increased)

Reviewer Comments:

Among these, the most plausible in terms of causality are restless legs syndrome and blood

phosphorus increased, which are discussed further below in section 8.3.5. Decreased vitamin D as defined here was reported in 8 burosumab (12%) versus 3 placebo (5%) patients based on 25-OH levels from baseline to week 12, and may be related to restoration of normal feedback homeostasis for vitamin D. Regarding the 4 to 1 ratio of burosumab to placebo incidence of blood PTH increased, the applicant did not consider that there was sufficient evidence of causality and this limited data is not sufficient to warrant labeling. Considering that laboratory data do not show an apparent effect of burosumab on iPTH levels (see below), this reviewer agrees that labeling of increased blood PTH as an adverse reaction is not warranted.

Laboratory Findings

Serum phosphorus, TmP/GFR and serum 1,25(OH)₂vitamin D are discussed as PD/efficacy endpoints in section 8.1; hyperphosphatemia is discussed as a safety endpoint in section 8.3.5.

Serum creatinine and eGFR are discussed in the safety section 8.3.5.

Serum iPTH

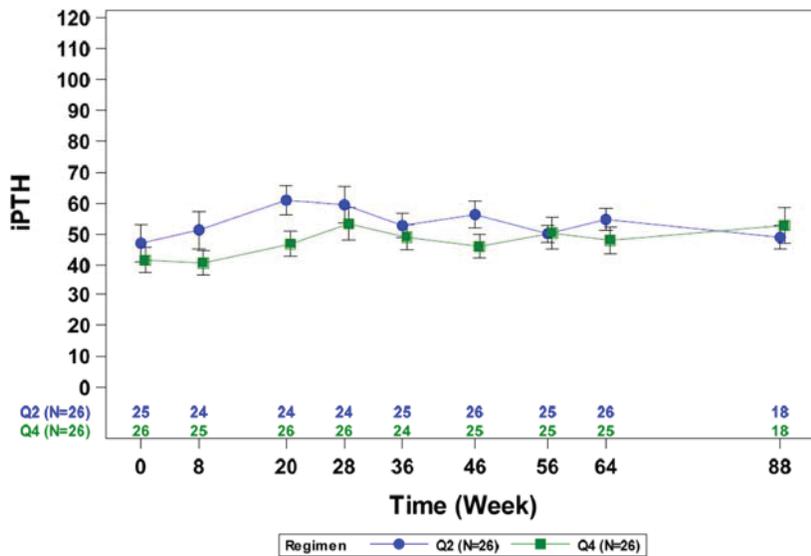
Pediatric

In study CL201, 9/52 patients had serum iPTH above the ULN (>59 pg/mL) at baseline. Patients with levels <2xULN at baseline showed steady levels of both calcium and iPTH with some fluctuation over time. Five patients had increases >2xULN (118 pg/mL); two of these also had high or high-normal serum calcium, suggesting autonomous parathyroid function:

- Patient # (b) (6), an 8 y/o male, had serum iPTH 119 pg/mL at baseline and other levels >2x ULN at weeks 8 and 28 (137 and 131 pg/mL), and high-normal calcium (max. 10.5 mg/dL). During longer-term treatment, iPTH tended to decline, with level of 59 pg/mL at week 88.
- Patient # (b) (6), a 10 y/o female, had elevated iPTH (83 pg/mL) and serum calcium (10.7 mg/dL) at baseline. During treatment to week 88, serum calcium remained above ULN (10.3 mg/dL) and serum iPTH fluctuated between 56-121 pg/mL. This patient had a TEAE of hypercalcemia (see below).

Mean serum iPTH in the overall study CL201 population showed no significant clinical trends over time:

Figure 51 Study CL201: Serum iPTH (pg/mL) (mean ± SE) (SAS)

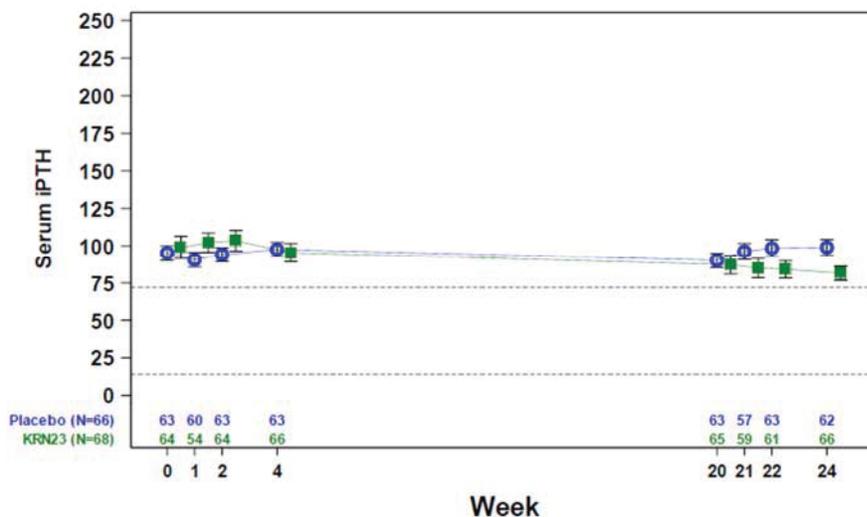


Source; CSR Fig. 12.6.1.2.1

Adult

In study CL303, mean serum iPTH was 97 pg/mL at baseline, which is above the ULN (>72 pg/mL); 4/134 patients (3%) gave a history of hyperparathyroidism pre-baseline. During the study there were minor changes in serum iPTH in both treatment groups:

Figure 52 Study CL303: Serum iPTH (pg/mL) (mean ± SE) (SAS)



Source: CSR Fig. 12.7.1.4.1

As reported in the 120 day safety update, one patient in this study (# (b)(6)), a 20 y/o male assigned to placebo, experienced an SAE of parathyroid tumor benign (verbatim parathyroid

adenoma) on study day 370. His serum iPTH was 102 pg/mL at baseline and ranged from 70-130 pg/mL through week 24; his serum calcium was 10.2 mg/dL at baseline and ranged from 9.3-10.8 mg/dL through week 24. After week 24 he began burosumab and at week 48 had serum iPTH of 79 pg/mL. At week 53 he had a serum calcium of 10.0 mg/dL and underwent parathyroidectomy, following which serum iPTH and Ca declined.

Reviewer Comments:

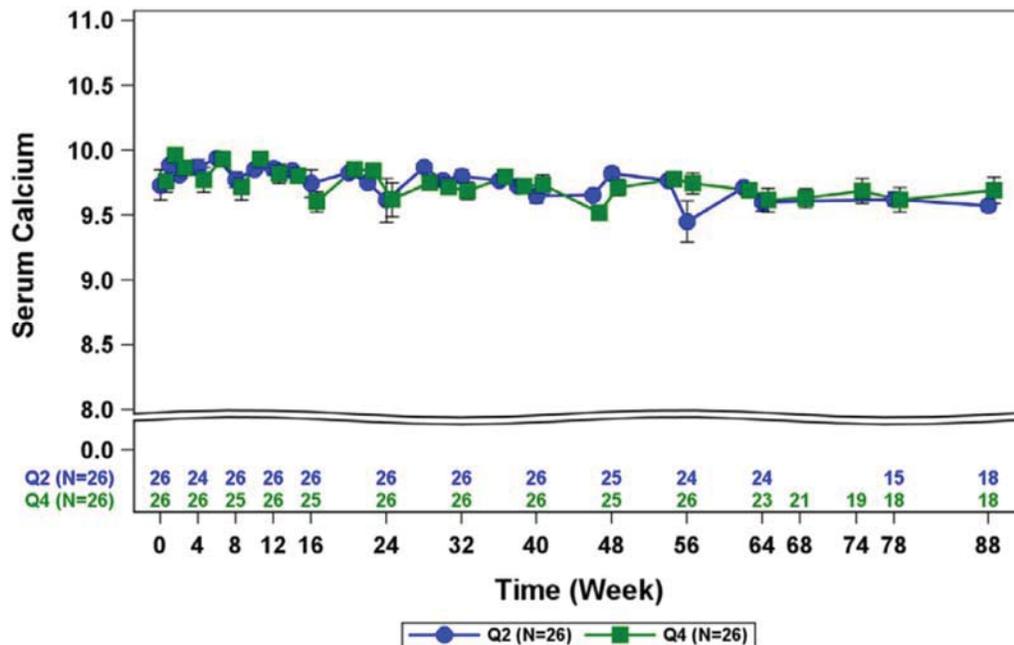
This patient and the two pediatric patients discussed likely had hyperparathyroidism (from previous conventional therapy) that preceded the respective studies. There were no TEAEs of hyperparathyroidism reported in any burosumab study. Serum iPTH levels fluctuated during the studies, but there was no evidence that burosumab causes or exacerbates hyperparathyroidism, unlike conventional therapy.

Calcium

Pediatric

In study CL201, there were no significant changes from baseline in serum calcium:

Figure 53 Study CL201: Serum calcium (mg/dL) (mean ± SE) (SAS)



Source: CSR Fig. 12.6.1.1.1

As noted above, there was one patient with elevated serum iPTH who also had a TEAE of hypercalcemia: patient # (b) (6), a 10 y/o female with elevated serum Ca at screening and baseline (10.7, 10.4 mg/dL); levels at weeks 1,2, and 4 were 10.9, 11.1 and 10.7 mg/dL. At the week 6 visit when the TEAE of hypercalcemia was recorded, the level was 11.3 mg/dL. Subsequent levels through week 88 ranged from 10.3-11.2 mg/dL. This patient also had a TEAE

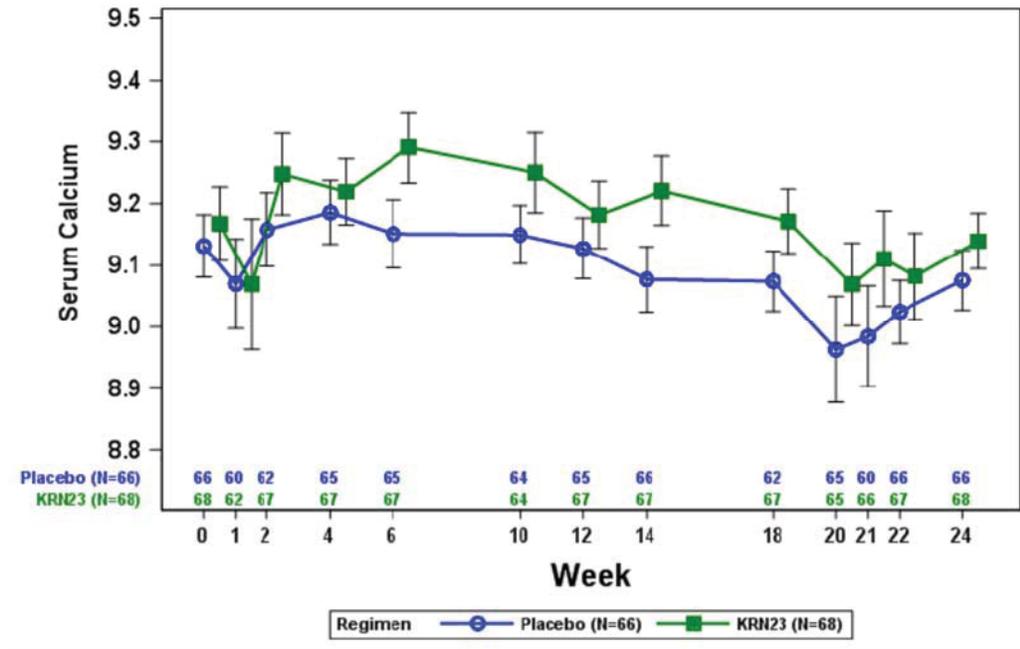
of increased 1,25(OH)D at week 54, with a level of 125 pg/mL, up from 48 pg/mL at baseline.

Mean 2-hour urine calcium/creatinine ratio demonstrated a moderate decreasing trend from baseline in study CL201; 24-hr urine calcium (mg/day) showed no trending changes during treatment.

Adult

In study CL303, there were no major changes from baseline in mean serum calcium in either treatment group during the double blind phase (figure below).

Figure 54 Study CL303: Serum calcium (mg/dL) (mean ± SE) (SAS)



Source: CSR Fig. 12.7.1.1.1

In study CL303, 2-hour urine calcium/creatinine ratio showed no trending changes over time.

Reviewer Comments:

Except for one pediatric patient who appeared to have preexisting hyperparathyroidism, there were no TEAEs of hypercalcemia in any of the pediatric or adult studies.

Serum FGF23

Serum FGF23 levels are elevated in nearly all untreated XLH patients (pediatric and adult). Levels increase further with conventional phosphate/calcitriol therapy (e.g. 2.3-fold increase in one study), demonstrating that feedback mechanisms are intact. Potentially, higher FGF23 may

blunt the effects of treatment or contribute to complications of treatment such as nephrocalcinosis. In addition, elevated free FGF23 has been associated with left ventricular hypertrophy (LVH) in patients with chronic kidney disease, and some XLH patients receiving oral phosphate are reported to have LVH.

In the burosumab studies, serum levels of FGF23 increased in all treated patients. As shown in the tables below, total FGF23 increased by ~1000-fold or greater in pediatric and adult patients (studies CL201 and CL203 respectively).

Table 87 Study CL201: Mean serum FGF23 levels (ng/mL) by timepoint

	Baseline	Week 8	Week 16	Week 28	Week 38	Week 64	Week 88	Week 112
n	52	52	52	51	50	52	35	12
Total FGF23	0.16	175	253	350	429	470	522	447
Source: CL201 CSR and ADLB								

Table 88 Study CL203: Mean serum FGF23 levels (ng/mL) by timepoint

	Baseline	Week 4	Week 8	Week 12	Week 24	Week 28	Week 36	Week 40	Week 48
N	20	20	20	20	20	19	20	18	20
Total FGF23	0.26	112	178	172	216	209	178	192	203
Source: CL203 CSR Table 14.2.1.3									

Reviewer Comments:

As the applicant indicates, these increases are likely due to a combination of increased secretion (e.g. from osteocytes) and reduced clearance of antibody-ligand (burosumab-FGF23) complexes. It is unclear whether there is any increase in free (unbound) serum FGF23; therefore, the clinical significance of the increased FGF23 is unknown and a safety issue of immunogenicity (e.g. ADCC, see nonclinical review section 5) cannot be ruled out. As noted below, echocardiograms in these studies have shown no evidence of LVH.

Serum amylase

In the pediatric studies, numerous patients had elevations of serum amylase at baseline or during treatment. When isoenzyme analysis was available, the predominant isoform was salivary. There were no TEAEs related to amylase or evidence of pancreatitis. In the adult study CL303, several patients had baseline amylase elevation, generally mild, and no patients shifted from Grade 1 to Grade 2 at week 24; mean serum amylase did not change from baseline in either the burosumab or placebo group.

Abnormal liver function tests

In study CL303, there was one AE of abnormal liver function test in patient # (b) (6), a 39 y/o female with past history of elevated GGT. At baseline, the patient had moderate elevations of serum ALT (90 U/L), AST (57 U/L), ALP (158 U/L) and GGT (144 U/L), with normal bilirubin (0.3 mg/dL); other serum chemistries and CBC were normal. The LFTs remained elevated through

week 48 of burosumab treatment with no increasing or decreasing trends. There were no other AEs related to liver disease.

Hematology

There were no clinically significant changes in any hematology parameters.

Vital Signs

Pediatric

Vital signs were measured at the start of visits after the patient was seated for 5 minutes. In study CL201, 4/52 patients showed a ≥ 15 mm Hg increase in systolic BP from baseline for 3 consecutive visits, which was suspected to be related to anxiety over blood draws and other procedures. Several parents were then recruited for home monitoring of BP; home and clinic readings did not substantially differ. Outliers for increase and decrease were similar for systolic BP but greater for increase vs. decrease for diastolic BP (35% vs. 8%). One patient (8 y/o male) had a TEAE of mild blood pressure increased at week 6, with BP of 123/62 (his screening and baseline BP were 123/68 and 112/69). Overall, means for systolic and diastolic BP and HR, including percentiles for sex and age, did not change during the course of studies CL201 or CL205.

Adult

In the double blind period of study CL303, mean changes from baseline to week 24 in burosumab and placebo groups were 0.1 and 1.0 mmHg for systolic BP, 0.5 and 1.3 mmHg for diastolic BP and 3.0 and -0.7 BPM for heart rate. Outliers were similar for increases and decreases in BP and HR within each treatment group.

Reviewer Comments:

There is no evidence that burosumab has any significant effect on vital signs in the pediatric or adult populations.

QT

Because burosumab is a monoclonal antibody and no signal was identified during the pre-clinical and clinical studies that would raise a concern for QT prolongation, a thorough QT/QTc study has not been conducted.

Electrocardiograms (ECGs)

ECGs were conducted at intervals in all pediatric and adult studies, with standardized procedures and central readings (treatment-blinded in study CL303). There were no clinically meaningful changes from baseline or between treatment groups in mean ECG parameters.

Burosumab, an IgG monoclonal antibody with molecular weight of 147 kD, is not anticipated to have a direct effect on cardiac ion channels. However, a monoclonal antibody may indirectly

prolong the QT interval through electrolyte changes, including hypocalcemia. Although burosumab was not demonstrated to cause significant hypocalcemia, changes in serum calcium may occur with fluctuations in serum phosphorus.

For the pediatric study CL201, ECG data for QT interval, corrected for heart rate using Fridericia's formula (QTcF), are summarized in the table below. The listed thresholds for absolute QTc and change from baseline QTc are those recommended by FDA guidance. In this study, none of the 52 patients had QTcF > 450 msec at baseline or at any post-baseline timepoint. There were 6 patients who had QTcF increases between 30-60 msec from baseline (maximum increase 44 msec), each at only one timepoint.

Table 89 Study CL201: Summary of QTcF data

	n	Mean (ms)	Min, max	# patients 450-480 ms	# patients >480-500 ms	# patients >500 ms	Mean change from baseline	Min, max	# patients 30-60 ms >baseline	# patients >60 ms >baseline
Baseline	52	390	357, 414	0	0	0				
Week 16	50	389	364, 412	0	0	0	-1.0	-25, +32	1	0
Week 40	52	392	366, 421	0	0	0	+2.3	-29, +31	1	0
Week 64	52	394	359, 416	0	0	0	+3.3	-22, +34	2	0
Week 88	36	393	369, 437	0	0	0	+4.1	-16, +44	2	0
Week 112	12	390	368, 406	0	0	0	+4.6	-17, +26	0	0

Sources: CSR Table 14.3.6.5.3, ADECG

In the pediatric study CL205, none of the 13 patients had a QTcF > 450 ms, nor an increase from baseline > 30 ms, at any point through week 40.

QTcF data for the adult study CL303 are summarized in the table below. One patient in each treatment group had a prolonged QTc (>450 ms) at baseline; none of the burosumab recipients had QTc > 450 ms post baseline. One burosumab and one placebo patient had QTc increase > 30 ms (35 ms and 32 ms respectively).

Table 90 Study CL303: Summary of QTcF data

	n	Mean (ms)	Min, max	# patients 450-480 ms	# patients >480-500 ms	# patients >500 ms	Mean change from baseline	Min, max	# patients 30-60 ms >baseline	# patients >60 ms >baseline
Burosumab										
Baseline	68	409	372, 451	1	0	0				
Week 24	67	408	373, 439	0	0	0	-1.0	-39, +35	1	0
Placebo										
Baseline	64	410	373, 463	1	0	0				
Week 24	66	410	370, 466	4	0	0	+0.5	-39, +32	1	0
Sources: CSR Table 14.3.6.3, ADEG										

According to the 120-day safety update, among all 176 adult patients with burosumab exposure across all studies, 9 (5%) had a maximal QTcF increase from baseline of 30-60 ms. None had an increase >60 ms or a QTcF>500 ms at any point.

Reviewer Comments:

QTc prolongation of >20 ms may be a clinical concern in children or adults. Although mean QTcF changes in these burosumab studies were much smaller, several patients had increases from baseline >30 ms. On the other hand, the similarity of burosumab/placebo data in study CL303 is reassuring. Overall, it appears unlikely that burosumab causes significant QT prolongation.

In study CL303, one patient (# (b) (6); placebo), a 28 y/o female with past history of WPW syndrome with palpitations, had a baseline ECG considered abnormal/ potentially clinically significant, and an SAE of palpitations at study day 332 (170 days after first burosumab dose), and underwent radiofrequency ablation for the WPW; ECG at subsequent week 48 visit showed NSR. (This was the only cardiac SAE in any study.)

Immunogenicity

Across all pediatric and adult XLH studies, no patients who were negative for anti-burosumab antibodies at baseline have tested positive for antibodies post-baseline. However, this may be related to limitations of the immunogenicity assay used (drug tolerance). A PMR will be required for reanalysis of banked samples (see Clinical Pharmacology, section 6) and analysis of whether immunogenicity is potentially related to any specific adverse events.

8.3.5. Analysis of Submission-Specific Safety Issues

Hyperphosphatemia

Pediatric

In the pediatric XLH studies, the normal range for serum phosphorus in children was defined in the study reports as 3.2-6.1 mg/dL. In study CL201, burosumab dose at 2 weeks post dose (“peak”) was titrated to a target of approximately the lower half of this range, initially designated as 3.5-4.5 mg/dL and later amended to 3.5-5.0 mg/dL. There were 5 patients with at least one phosphorus level >4.5 mg/dL, 3 of whom (# [REDACTED]^{(b) (6)}) had dose reductions for levels 4.6-4.9 mg/dL, following which levels declined. Patient # [REDACTED]^{(b) (6)} had the highest level in the study of 5.2 mg/dL at week 48 (and the only pediatric TEAE for “blood phosphorus increased”), but subsequent levels were 3.3-4.3 mg/dL without a dose reduction. In study CL205, one patient (# [REDACTED]^{(b) (6)}) out of 13 had serum phosphorus >4.5 mg/dL, with levels of 4.9 and 4.6 mg/dL at weeks 15 and 20.

Adult

In the initial adult studies, normal range for serum phosphorus was designated as 2.5-4.5 mg/dL, and dose was titrated to achieve level of 2.5 - 3.5 mg/dL. In studies INT-001/002, there were no instances of serum phosphorus above ULN (>4.5 mg/dL), and in study CL203, one patient had a single elevated level of 4.9 mg/dL which returned to normal range with lowering of the dose.

In study CL303, the initial dose of 1.0 mg/kg (the highest of the doses previously used in adults) was to be reduced per protocol by half if a patient had a serum phosphorus >5.0 mg/dL, or two levels >4.5 mg/dL. During the double-blind period, 9 patients in the burosumab group (13%) had high serum phosphorus (> 4.5 mg/dL), including 5 who had repeat elevations and underwent dose reduction to 0.5 mg/kg. Four of these patients had dose reductions at weeks 4, 12, 12 and 16 and subsequently maintained normal serum phosphorus levels. Three of these events were designated as AEs of blood phosphorus increased, and the other event, in which a patient had the highest levels in the study of 6.2 mg/kg at weeks 1 and 2 after the first injection, was designated an AE of hyperphosphatemia. One patient ([REDACTED]^{(b) (6)}) required 3 successive dose reductions (to 0.5, 0.3, 0.2 mg/kg at weeks 8, 20 and 28, respectively) because serum phosphorus remained in 4.6-5.5 mg/dL (elevated) range.

In the placebo group of study CL303, no patient had high serum phosphorus during the double-blind period. After crossing over to burosumab at week 24, the original BLA submission reported that 5 patients had high levels (4.9-6.1 mg/dL) at week 26 and 3 of these then had dose reduction to 0.5 mg/kg (and TEAE designation of hyperphosphatemia). Subsequently the 120-day update reported that 3 additional patients in this arm had levels of 4.6-4.9 mg/dL at week 34 through 46, but did not require dose reduction.

Reviewer Comments:

In the pediatric studies, no patient had an adverse event of hyperphosphatemia, but 6/62 patients had serum phosphorus levels in the upper-mid range of 4.6-5.2 mg/dL and 3 of these

patients had dose reductions. In the adult studies, the ULN is lower (4.5 mg/dL), and 17/134 patients had ≥ 1 elevated level, including 8 who had dose reductions. It is clearly important that patients beginning burosumab (pediatric or adult) have serum phosphorus monitored during at least the first 3 months of treatment, as dose reduction may be needed.

Ectopic mineralization

Patients with XLH frequently develop ectopic calcifications in the kidney (nephrocalcinosis and/or nephrolithiasis) or cardiovascular tissues; this is believed to result mainly from treatment with oral phosphate and active vitamin D, rather than the underlying XLH. Nonclinical data have shown that burosumab-related hyperphosphatemia may also result in ectopic mineralization (see section 5); therefore, clinical study patients have been routinely monitored with renal ultrasound and echocardiogram. Renal ultrasound is used to evaluate the presence of nephrocalcinosis based on a 5-point scale:

- 0 = Normal
- 1 = Faint hyperechogenic rim around the medullary pyramids
- 2 = More intense echogenic rim with echoes faintly filling the entire pyramid
- 3 = Uniformly intense echoes throughout the pyramid
- 4 = Stone formation: solitary focus of echoes at the tip of the pyramid

TEAEs of ectopic mineralization were identified by a MedDRA search of “calcification” which included 50 preferred terms as listed in the ISS SAP.

Some laboratory parameters relevant to potential ectopic mineralization (serum and urine calcium and serum iPTH) are discussed in section 8.3.4 above; renal function parameters (serum creatinine, eGFR) are discussed below.

Pediatric

In Study CL201 patients, nearly all of whom had prior treatment with phosphate and active vitamin D, renal ultrasound nephrocalcinosis scores at baseline were 0, 1, and 2 for 65%, 21%, and 14% of patients, respectively. A score of ≥ 3 at baseline was an exclusion criterion; there were 3 patients who were not enrolled on this basis.

During burosumab treatment, as of the 5/18/17 data cutoff for the 120-day safety update, scores were unchanged from baseline in 36/52 patients (69%); decreased by 1 point in 3/52 patients (6%); and increased by 1 point in 13/52 patients (25%). There were no patients with changes in scores that were >1 point in either direction (see table below). Changes occurred at various times between week 16 and week 136. The incidence of such changes was similar in patients randomized to Q2W compared to Q4W dosing.

Table 91 Study CL201: Patients with changes from baseline in nephrocalcinosis scores

Patient #	Treatment group	Screening/ baseline	Week 16	Week 40	Week 64	Week 88	Week 112	Week 136
		Nephrocalcinosis score at timepoint						
Patients with decrease in nephrocalcinosis score								
(b) (6)	Q2W	1	0	0	0	0	0	0
	Q4W	1	1	0	0	0	0	0
	Q4W	1	1	1	1	1	0	
Patients with increase in nephrocalcinosis score								
(b) (6)	Q4W	0	1	1	1	1		
	Q4W	0	0	0	0	1		
	Q2W	0	0	0	0	0	1	
	Q2W	0	0	0	0	0	1	
	Q2W	0	0	0	0	0	0	1
	Q4W	1	2	2	2	2	2	
	Q2W	1	1	2	2	2		
	Q2W	1	1	2	2	2	2	
	Q2W	1	1	1	2	2	2	
	Q4W	1	1	1	1	1	1	2
	Q2W	2	2	2	3	3	3	
	Q4W	2	2	2	3	3		
	Q4W	2	2	2	2	2	3	

Source: 120 day safety update Listing 14.1.3.6.3

For the week 64 report of this study, the applicant conducted post hoc analyses of the 7 patients who had post baseline score increases at that cutoff date, compared to the other 45 patients. The 7 patients with increasing scores generally had higher iPTH levels and higher urinary calcium excretion at baseline, but changes in these parameters to week 64 during treatment were generally similar between two subgroups. One patient (# (b) (6)) with an increase in renal ultrasound score from 1 to 2 between baseline and week 16 had hypercalcemia at week 6 (11.3 mg/dL), and mild elevations of serum calcium and/or iPTH at baseline and intermittently during treatment.

For the 13 patients in the above table with increases in nephrocalcinosis score as of the safety update, mean eGFR at baseline was 156 mL/min at baseline, compared to 168 mL/min in the other 39 patients whose nephrocalcinosis scores did not change or improved. Changes in eGFR during treatment were similar in these two groups: in the 13 patients with worsening on ultrasound, the last recorded eGFR value ranged from 19% below to 27% above baseline, with mean change from baseline of +1.4%; whereas in the 39 patients with no change or improvement on ultrasound, the last eGFR ranged from 31% below to 39% above baseline, with mean change of +2.5%. Of the 13 patients with increases in nephrocalcinosis scores, the most concerning decline was seen in Patient # (b) (6), with an increase from 2 to 3 between weeks

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(burosumab - twza)

40 and 64. This patient had a decline in eGFR from 181 mL/min at baseline to 165 mL/min at week 64 and 162 mL/min at week 88, but no consistent changes in urine or serum calcium, and a substantial decline in serum iPTH.

In study CL205, renal ultrasound scores were 0 for each of the 13 patients, both at baseline and at week 40.

Across both pediatric studies, there was one patient (# [REDACTED]^{(b) (6)} in study CL201) with a reported TEAE of nephrocalcinosis at week 40. However, this was based on a local ultrasound read that was not confirmed by central review: all ultrasound scores by central reading for this patient were 0 (at baseline and weeks 16, 40, 64, 88 and 112).

Echocardiograms are conducted about every 24 weeks in study CL201. All 52 patients had no ectopic calcifications on the baseline echo. There were two patients with positive echo findings post baseline as reported in the safety update: patient # [REDACTED]^{(b) (6)} (Q4W group) with grade 1 ectopic mineralization at week 88 but not at week 112 (grade 0); and patient # [REDACTED]^{(b) (6)} (Q2W group) with grade 1 ectopic mineralization at week 88, the last assessment. Both patients had normal serum calcium and iPTH at all visits, and no renal calcifications (nephrocalcinosis or nephrolithiasis) on any ultrasound during the treatment period. LV mass indices were normal at baseline and remained stable through week 88, indicating no evidence of LVH.

Adult

In study CL303, fewer than half of patients had renal ultrasound scores of 0 at baseline, most likely due to extensive prior treatment with phosphate/calcitriol (average cumulative exposure for enrolled patients was ~20 years). In the 24-week double-blind phase, 1-point reduction from baseline in nephrocalcinosis scores (i.e. improvement) occurred in 4 placebo and 4 burosumab patients; 1-point increase from baseline (i.e. worsening) occurred in 12 placebo and 11 burosumab patients (table below). As in the pediatric study, there were no larger changes ($\geq +2$ or ≤ -2). None of the patients with increasing scores exhibited an increase in urinary calcium, any clinically meaningful changes in iPTH or decrease in eGFR. The 120-day safety update, which includes some week 48 ultrasound data from this study, indicates that among all 134 study patients, 23 (17%) had a 1-point increase from baseline to the last exam before the data cutoff, while 5 patients (4%) had a 1-point decrease.

Table 92 Study CL303: Shifts in nephrocalcinosis score from baseline at week 24 – double blind period

Baseline score	Baseline N	Nephrocalcinosis score at week 24				
		0	1	2	3	NA or missing
Placebo						
0	27	18	9	0	0	0
1	32	3	26	3	0	0
2	7	0	1	6	0	0
3	0	0	0	0	0	0
Burosumab						
0	34	23	9	0	0	2
1	23	4	18	1	0	0
2	9	0	0	8	1	0
3	2	0	0	0	1	1

Source: Summary of Clinical Safety Table 2.7.4.2.1.6.5.2.1.1

As of the cutoff for the 120-day safety update, there were 6 TEAEs of nephrocalcinosis in study CL303: 4 were based on the week-24 ultrasound (3 placebo, 1 burosumab), and 2 were based on the week-48 ultrasound (1 prior-placebo, 1 continuous-burosumab). There were no TEAEs of nephrocalcinosis reported in safety data from the other adult studies (see Table 91 below).

Nephrolithiasis was detected on baseline ultrasound in 3 placebo and 3 burosumab patients, and was no longer present on the week 24 ultrasound in any of these patients. Conversely, there were 2 placebo and 5 burosumab patients with nephrolithiasis seen at week 24 that had not been present on the baseline exam.

As of the cutoff for the 120-day safety update, there were 3 TEAEs of nephrolithiasis in study CL303 (1 placebo, 2 burosumab), all of which were based on the week-24 ultrasound. There were also 3 TEAEs of nephrolithiasis in the phase 2 studies:

- In study INT-001, patient # (b) (6) passed 2 kidney stones on day 150 and discontinued the study. Subsequently this patient enrolled in study CL203 (now patient # (b) (6)) and passed a small kidney stone on day 1492 (from enrollment in INT-001)
- In study CL203, patient # (b) (6) had a L kidney stone on day 1731
- In study CL203, patient # (b) (6) had a kidney stone on day 1528

In addition, patient # (b) (6) (study CL203) developed calcifications in the pancreatic head on CT on day 2005 of cumulative burosumab exposure.

Table 93 Ectopic Mineralization AEs in adult studies

Preferred term Subject incidence – n (%)	Study CL303		Total Buros* (N=134)	Study CL304	Study CL203	Studies INT- 001/002	Overall Buros
	Double blind (wk 0-24) Placebo (N=66)	Buros (N=68)		N=14	N=20	N=28	N=176
Patients with TEAEs, n (%)	0	0	9 (7)	0	4 (20)	1 (4)	13 (7)
Number of TEAEs	0	0	9	0	4	1	14
Nephrocalcinosis, n (%)	0	0	6 (5)‡	0	0	0	6 (4)
Nephrolithiasis, n (%)	0	0	3 (2)‡	0	3 (15)	1 (4)	6 (4)
Pancreatic calcification	0	0	0	0	1 (5)	0	1 (0.6)

*All patients who received burosumab in study CL303; length of burosumab treatment varies as it includes both patients randomized to burosumab, and patients randomized to placebo who crossed over to burosumab at week 24
 ‡ In study CL303, 4 TEAEs of nephrocalcinosis (3 placebo, 1 burosumab) and 3 TEAEs of nephrolithiasis (1 placebo, 2 burosumab) were based on week 24 ultrasound which was conducted on the first day of open label burosumab, and the Applicant assigned these TEAEs to the open label rather than double blind phase
 Data as of 120 day safety update cutoff of 6/8/17 for ongoing studies (CL303, CL304, CL203)
 Source: ISS Safety Update Table 14.2.3.1.28

Reviewer Comments:

It is reassuring that nephrocalcinosis score changes were similar in placebo and burosumab groups in study CL303 and that no changes were greater than 1 point, which the applicant believes is within the intrinsic variability of the exam. However, there were more patients with score increases than decreases, and the 24-week duration of this double blind phase may be too limited for definitive evaluation of a possible association of burosumab therapy and nephrocalcinosis. In pediatric study CL201, there were 13 children with nephrocalcinosis score increases and only 3 with decreases, and most of the changes appeared at week 40 or later. Thus, the data do not rule out the potential for development of nephrocalcinosis with long-term burosumab exposure. There were also several patients who developed nephrolithiasis during treatment, and an increased risk cannot be ruled out.

Echocardiogram evaluations were conducted at baseline and week 24 in study CL303, with semi-quantitative scoring for ectopic calcifications (eCS). In the burosumab group, there were more patients with improvements in calcification than with worsening (3 vs. 1) while the reverse was seen in the placebo group (1 vs. 7). There were no patients with large changes (≥1 point difference from baseline). There was no evidence of development of LVH.

Renal function

Renal function was monitored in clinical studies via periodic serum creatinine and BUN, eGFR (Bedside Schwartz equation) and urinalysis. The primary concern in regard to the kidneys has been mineralization, based on burosumab pharmacology and toxicity study findings. In addition, during the review of this BLA a concern was raised about potential antibody-

dependent cellular cytotoxicity (ADCC) based on an *in vitro* assay. The putative mechanism would involve binding of circulating burosumab-FGF23 complexes to the FGFR1 co-receptor, α -klotho, which is expressed in proximal and distal renal tubule cells; and subsequent attack by NK effector cells (see nonclinical review, section 5).

Pediatric

In study CL201, there was minimal change from baseline to week 64 in mean eGFR (165 and 170 mL/min/1.73 m² respectively), or in mean serum creatinine (0.43, 0.44 mg/dL), or BUN (13.0, 11.2 mg/dL). In study CL205, there was minimal change from baseline to week 40 in mean eGFR (188, 183 mL/min/1.73 m²), or in mean serum creatinine (0.28, 0.29 mg/dL).

There were 3 pediatric patients with AEs potentially related to renal dysfunction, following an SMQ-targeted search reported in the 120-day safety update:

- Study CL201, patient # (b) (6): a 7 y/o female with history of vesicoureteric reflux, had an increase in serum creatinine from 0.5 mg/dL at baseline to 0.9 mg/dL at week 46 (reference range 0.2-0.6 mg/dL), concurrent with mild hyponatremia; this was reported as a TEAE of **blood creatinine increased**. These parameters had apparently normalized within 2 weeks at which time (week 48) the patient developed SAEs of pyrexia and myalgia (see section 8.3.4 on SAEs above). At subsequent visits (weeks 56, 64, 88) the serum creatinine was normal (0.5-0.6 mg/dL).
- Study CL201, patient # (b) (6): a 5 y/o male, experienced a TEAE of **proteinuria** at week 136, considered mild and not related to burosumab (see below). Serum creatinine was in the normal range at all visits.
- Study CL205, patient # (b) (6): a 3 y/o male, experienced TEAEs of **polyuria** and **polydipsia** on study day 2 which resolved without treatment after 2 weeks; serum glucose and creatinine were normal throughout the study period.

None of these 3 patients had any increase in nephrocalcinosis scores. Except for patient # (b) (6), no pediatric patient had clinically significant changes in serum creatinine or eGFR.

Because of the distribution of α -klotho in renal tubule cells, any burosumab-related ADCC would be expected to cause renal tubular rather than glomerular damage. Renal tubule toxicity alone has a small effect on eGFR (serum creatinine is to some extent secreted across the proximal tubule) but may cause substantial proteinuria; therefore, urinalysis data may be relevant. The following table lists all patients in study CL201 with proteinuria ($\geq 1+$ on dipstick UA) at any visit. As noted above, one patient (# (b) (6)) had a reported AE of proteinuria, but this was present at baseline. There were 9 patients with negative or trace testing at baseline, and a post-baseline result of 1+. Among these only patient # (b) (6) had an increase in nephrocalcinosis score by ultrasound (2 at week 88, to 3 at week 112); his serum creatinine was stable at 0.4-0.5 mg/dL throughout the study. No patient had 2+ or greater proteinuria past baseline.

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Table 94 Study CL201: Patients with proteinuria (≥1+ on dipstick UA) at any visit

	Screening	Baseline	Week 8	Week 16	Week 24	Week 40	Week 46	Week 64	Week 88	Week 112
(b) (6)		Neg	Trace	1+	Trace	Neg	Trace	Trace	1+	Trace
		2+		Neg	Neg	Neg	Neg	Neg	Neg	Neg
		1+	Neg	Neg	Trace	Neg	Trace	Neg	Trace	Neg
		2+	Neg	Trace	1+	Trace	1+	1+	Trace	Trace
		Neg	Neg	Neg	Neg	Neg	Neg	1+	Neg	Neg
		Neg	Neg	Neg	Neg	Neg	Neg	Trace	Neg	1+
		Neg	Neg	Neg	Trace	Neg	Trace	Trace	Neg	1+
		Neg	Neg	Neg	Neg	Neg	Neg	1+	Neg	
		Neg	Neg	Neg	Neg	Neg	Neg	1+	Neg	
		Trace	1+	Neg	Trace	Trace	Neg	Neg		
		Neg	1+	Neg	Neg	Trace	Neg	Neg	Trace	Neg
		Neg	Trace	1+	1+	Neg	1+	Neg	1+	
		Neg	Trace	Neg	Neg	Neg	Neg	Neg	1+	Trace

Source: CL201 ADLB

Adult

In study CL303, mean eGFR was stable in both double blind groups from baseline to week 24: in the burosumab group, 114.5 to 114.1 ml/min/1.73 m²; and in the placebo group, 117.0 to 119.0 mL/min/1.73 m². For the overall study population, mean eGFR was 115.7 mL/min/1.73 m² at baseline and 117.1 mL/min/1.73 m² at week 48 (open label phase). Mean serum creatinine similarly showed no trends over time in this study, or in studies CL304 or CL203 through the safety update cutoffs.

Among all adult studies (total N=176), there were 5 patients with potentially relevant renal TEAEs, as reported by the applicant in the safety update. Two of these events (blood creatinine increased; GFR decreased) occurred, respectively, at study baseline and while the patient was receiving blinded placebo, and in each case there was subsequent improvement in renal parameters during burosumab treatment. No other patients had AEs related to renal functional impairment.

In study CL303, there were 5 patients (3 burosumab, 2 placebo) who exhibited proteinuria (≥1+ on dipstick UA) during the 24-week double blind phase following a negative or trace reading at baseline (table below). Two additional patients developed proteinuria at week 36 (open label phase). These patients had no significant changes in serum creatinine.

Table 95 Study CL303: Patients with proteinuria (≥1+ on dipstick UA) at any visit

Treatment group	Pt #	Baseline	Wk 4	Wk 12	Wk 24	Wk 36
Burosumab	(b) (6)	Trace	Trace	Neg	Neg	2+
		Neg	Neg	Neg	1+	
		Neg	Neg	1+	Neg	
		Trace	Neg	Neg	Neg	1+
		Neg		1+	2+	
Placebo		Neg	Neg	Neg	1+	
		1+	2+	1+	Neg	Neg
		Neg	Neg	2+		

Source: CSR ADLB

Reviewer Comments:

Based on data collected in these studies, there is no evidence of an association of burosumab with acute renal toxicity. However, the testing conducted may not be adequately sensitive to detect renal damage from mechanisms other than mineralization. Renal tubular damage (e.g. from ADCC) in particular may require more specialized testing such as quantitative urine protein or other chemistries over a longer duration of treatment. This should be further investigated in a PMR (see section 12).

Injection site reactions

Pediatric

Injection site reactions (ISRs) was the most frequent category of adverse events in the pediatric studies. As of the original BLA cutoff dates, the subject incidence of ISRs across combined studies CL201 and CL205 was 57%. Among those affected, the mean number of ISRs per patient was 5.7. In study CL201, incidence was greater with the Q2W regimen (73%) compared with Q4W (58%) presumably because of the greater number of injections. ISRs were less frequent in study CL205, occurring in 3 patients (23%); the applicant believes this is because of smaller injection volumes in the younger patients.

In the original BLA ISS, the time to onset of the first ISR was evenly distributed from baseline to week 76, with a mean of 30 weeks. Nearly all ISRs (97%) occurred within 1 day of an injection; 91% resolved within 3 days, and 98% had resolved. All ISRs were Grade 1 (mild), and none resulted in study drug discontinuation. Erythema was the most common symptom; the most frequent AE terms are listed in the table below. There were no significant changes in the 120-day safety update; the overall subject incidence in children was 58.5%, minimally different from the original BLA safety dataset.

Table 96 Injection site reactions (ISR) in pediatric studies

Preferred term	Study CL201			Study CL205	Overall
	Q4W*	Q2W	Total	Q2W	
Subject incidence – n (%)	N=26	N=26	N=52	N=13	N=65
Patients with ISR, n (%)	15 (58)	19 (73)	34 (65)	3 (23)	37 (57)
Number of ISR TEAEs	91	117	208	3	211
Injection site reaction	11 (42)	10 (39)	21 (40)	1 (8)	22 (34)
Injection site erythema	8 (31)	12 (46)	20 (39)	1 (8)	21 (32)
Injection site pruritis	4 (15)	2 (8)	6 (12)	1 (8)	7 (11)
Injection site swelling	1 (4)	5 (19)	6 (12)	0	6 (9)
Injection site pain	2 (8)	2 (8)	4 (8)	0	4 (6)
Injection site rash	2 (8)	2 (8)	4 (8)	0	4 (6)
Injection site bruising	1 (4)	2 (8)	3 (6)	0	3 (5)

The most frequent event terms (>1 patient with reported AE) within ISR HLT are listed.
 *Patients randomized to Q4W, but switched to Q2W after week 64
 Data as of 12/1/16 and 1/6/17 cutoffs for CL201 and CL205 studies respectively
 Source: ISS Table 14.1.3.1.19

Adult

ISRs were much less common in adult compared to pediatric patients. In the 24-week double blind phase of study CL303, ISRs were reported in 8 placebo and 8 burosumab patients (12%). Incidence in the overall adult burosumab population (N=176) was 14.2%. Most ISRs occurred in the first week of treatment, but some first episodes occurred after 24 weeks. Duration was ≤3 days in 82% of events, and all were reported to have resolved, although one patient in study INT-001 discontinued due to injection site urticaria. The most common injection site symptom was erythema, followed by pain and pruritis.

According to the 120-day safety update, the subject incidence of ISRs in adults increased from the original 14.2% to 25%, attributable to the large increase in total adult exposure duration between these two reports. Although mean exposure duration in adults remained shorter than in children (60 vs. 108 weeks), a large discrepancy in ISR incidence (25% vs. 58%) persisted, with no explanation. Because the ISR incidence was the same with burosumab and placebo in study CL303, and composition of the respective injections was identical except for the presence or absence of burosumab, it does not appear that the drug itself is a local irritant but may be a result of an excipient.

Hypersensitivity

In the applicant’s analyses, patients with a potential immune reaction to burosumab were identified by searching preferred terms in the narrow SMQ for “hypersensitivity”, which are listed in the ISS SAP. ADA data are discussed above (section 6.4.4).

Pediatric

In studies CL201 and CL205, this SMQ identified 25 patients (39%) with 49 events, mostly related to rash and other skin reactions (table below). Urticaria was reported in 3 patients (5%) and lip swelling and swelling face were reported in 1 patient each. All events were mild or moderate (Grade 1 or 2) except for one Grade 3 event of severe rash attributed to swimming in a lake. There were no reports of angioedema or anaphylactic reaction, and none that were SAEs or that led to discontinuation.

Table 97 Hypersensitivity AEs in pediatric studies

Preferred term Subject incidence – n (%)	Study CL201			Study CL205	Overall N=65
	Q4W* N=26	Q2W N=26	Total N=52	Q2W N=13	
Patients with hypersensitivity TEAEs, n (%)	13 (50)	10 (39)	23 (44)	2 (15)	25 (39)
Number of hypersensitivity TEAEs	29	18	47	2	49
Rash	6 (23)	7 (27)	13 (25)	1 (8)	14 (22)
Injection site rash	2 (8)	2 (8)	4 (8)	0	4 (6)
Urticaria	1 (4)	1 (4)	2 (4)	1 (8)	3 (5)

The most frequent event terms (>2 patients with reported AE) identified by hypersensitivity SMQ are listed.
 * Patients randomized to Q4W, but switched to Q2W after week 64
 Data as of 12/1/16 and 1/6/17 cutoffs for CL201 and CL205 studies respectively
 Source: ISS Table 14.1.3.1.22

In the safety update, 3 study CL201 patients had recurrences of hypersensitivity AEs 1-2 years later:

- Patient # (b) (6), a 5 y/o male, with previous AEs of swelling face on study days 1 and 171, had another AE of swelling face (mild) on day 837, and an AE of gingival abscess (moderate) on day 844. Both events resolved.
- Patient # (b) (6), an 8 y/o female, had urticaria on day 97 and cold urticaria on 547

- Patient # (b) (6), an 11 y/o female, had urticaria (legs and back) and swollen lip on day 28 following her second injection; both events were mild and resolved in 2-3 days. On day 472 the patient had another AE of urticaria, also mild and resolved.

Also reported in the 120-day update was a patient in study CL205 (# (b) (6)) who experienced AE of swelling face on day 251, related to an SAE of tooth abscess (see section 11.4.2).

Adult

In the adult studies, potential hypersensitivity events identified by the SMQ were reported in 21 of the overall 176 patients (12%). In study CL303 double blind phase, 4 patients (6%) in each group (burosumab and placebo) had such events. The only event with severity grade >2 was life-threatening angioedema in a 68 y/o female in study CL203 who experienced throat tightening, swollen face and tongue which was attributed to lisinopril; the patient is continuing burosumab without further incident (see section 8.3.4, SAEs). There were no reports of anaphylactic reactions. One patient in study INT-001 discontinued due to a hypersensitivity reaction (injection site urticaria).

Table 98 Hypersensitivity AEs in adult studies

Preferred term Subject incidence – n (%)	Study CL303			Study CL304 N=14	Study CL203 N=20	Studies INT- 001/002 N=28	Overall Buros N=176
	Double blind (wk 0-24)		Total Buros* (N=134)				
	Placebo (N=66)	Buros (N=68)					
Patients with hypersensitivity TEAEs	4 (6)	4 (6)	7 (5)	4 (29)	3 (15)	7 (25)	21 (12)
Number of TEAEs	4	4	8	7	3	10	28
Rash	3 (5)	0	1 (<1)	0	0	1 (4)	2 (1)
Urticaria	1 (1.5)	0	0	0	0	0	0
Urticaria contact	0	1 (1.5)	1 (<1)	0	0	0	1 (<1)
Dermatitis contact	0	1 (1.5)	1 (<1)	0	0	2 (7)	3 (2)
Injection site rash	0	1 (1.5)	1 (<1)	0	0	1 (4)	2 (1)
Eczema	0	1 (1.5)	1 (<1)	0	0	0	1 (<1)

Table includes all hypersensitivity AEs in double blind phase of study CL303
 *All patients who received burosumab in study CL303; length of burosumab treatment varies as it includes both patients randomized to burosumab, and patients randomized to placebo who crossed over to burosumab at week 24
 Data as of cutoff dates of 8/18/16, 12/22/16 and 12/13/16 for ongoing studies CL203, CL303, CL304
 Source: ISS Table 14.2.3.1.22

The 120-day safety update reports that 4 additional patients had experienced hypersensitivity AEs: 3 patients with urticaria and one patient with facial swelling that was concurrent with a toothache.

At this time, given that the assay for immunogenicity is still under evaluation, this dataset will be reevaluated after an optimal immunoassay is developed and samples are reanalyzed.

Restless legs syndrome

Restless leg syndrome (RLS) is a neurological disorder characterized by unpleasant sensations in the legs and an uncontrollable urge to move them. The etiology of RLS is unknown, but a genetic component has been proposed. RLS is associated with various conditions including diabetes, kidney failure, thyroid disease, electrolyte imbalances and use of certain medications. It is highly associated with chronic hyperphosphatemia in renal dialysis patients and is reversible with dialysis. Thus, increasing serum phosphorus levels in chronically hypophosphatemic XLH patients may be expected to incite RLS symptoms in predisposed patients.

There were no reports of restless legs syndrome (RLS) in the pediatric studies.

In study CL303, two patients in each group (placebo, burosumab) had a prior history of RLS; one of these in each group had a TEAE of worsening RLS. During the double blind period, a total of 8 (12%) patients in the burosumab group and 5 (8%) patients in the placebo group had a TEAE of RLS or limb discomfort (table below). Across all adult studies, 16/176 (9%) patients reported TEAEs of RLS during burosumab treatment, including 4 patients with a prior history of RLS. One patient, a 38 y/o female in study INT-001/002, had a Grade 3 event of worsening RLS which led to her discontinuation from the study; subsequently she enrolled in study CL203 and had no reported RLS through week 48. None of these events appear sufficient to warrant a concern that needs further assessment at this time.

Table 99 Restless legs syndrome AEs in adult studies

	Study CL303			Study CL304	Study CL203	Studies INT-001/002	Overall Buros
	Double blind (wk 0-24)		Total Buros* (N=134)				
Preferred term Subject incidence – n (%)	Placebo (N=66)	Buros (N=68)			N=14	N=20	N=28
Patients with TEAEs, n(%)	5 (8)	8 (12)	10 (8)	1 (7)	0	5 (18)	16 (9)
Number of TEAEs	5	8	10	1	0	9	20
Grade 3 severity	0	0	0	0	0	1 (4)	1 (0.6)
Restless legs syndrome	4 (6)	8 (12)	10 (8)	1 (7)	0	5 (18)	16 (9)
Limb discomfort	1 (1.5)	0	0	0	0	0	0
*All patients who received burosumab in study CL303; length of burosumab treatment varies as it includes both patients randomized to burosumab, and patients randomized to placebo who crossed over to burosumab at week 24 Data as of cutoff dates of 8/18/16, 12/22/16 and 12/13/16 for ongoing studies CL203, CL303, CL304 Source: ISS Tables 14.2.3.1.31							

8.3.6. Safety Analyses by Demographic Subgroups

Pediatric safety data were analyzed by sex and race subgroups and did not show major differences between males and females (table below). Few non-whites were studied (7/65

=11%) limiting interpretation of race subgroup analysis (ISS Table 14.1.3.1.8).

Table 100 Most frequent pediatric AEs by gender (SAS)

Preferred term Subject incidence: n (%)	Male N=33	Female N=32	Overall N=65
Cough	20 (61)	16 (50)	36 (55)
Headache	18 (55)	17 (53)	35 (54)
Pain in extremity	13 (39)	14 (44)	27 (42)
Nasopharyngitis	13 (39)	13 (41)	26 (40)
Upper respiratory tract infection	12 (36)	14 (44)	26 (40)
Vomiting	9 (27)	16 (50)	25 (39)
Pyrexia	11 (33)	13 (41)	24 (37)
Source: ISS Table 2.7.4.2.1.1.2			

In the adult study CL303, female patients had a higher incidence of arthralgia with placebo compared to burosumab (30% vs. 9%); other AEs were generally balanced between treatment groups (table below). Male patients were more likely to experience restless leg syndrome with burosumab (17%, vs. none w/ placebo), with no other apparent gender imbalances between gender.

Table 101 Most frequent adult AEs by gender (study CL303 double blind phase, week 0-24)

Preferred term Subject incidence: n (%)	Male		Female	
	Placebo N=23	Buros N=24	Placebo N=43	Buros N=44
Any TEAE	21 (91)	21 (88)	40 (93)	43 (98)
Arthralgia	3 (13)	2 (8)	13 (30)	4 (9)
Nasopharyngitis	4 (17)	3 (13)	2 (5)	6 (14)
Back pain	3 (13)	4 (17)	3 (7)	6 (14)
Headache	0	2 (8)	5 (12)	6 (14)
Pain in extremity	4 (17)	2 (8)	6 (14)	3 (7)
Restless legs syndrome	0	4 (17)	4 (9)	4 (9)
Source: ISS Table 14.99.2.3.1.13.1				

In study CL303, both patients ≤ 50 and > 50 years were more likely to have arthralgia with placebo compared to burosumab. Older patients were more likely to have restless legs syndrome with burosumab (5 vs. 1 patient, 31% vs. 8%); this is consistent with the incidence of restless legs syndrome in the general population.

Table 102 Most frequent adult AEs by age group (study CL303 double blind phase, week 0-24)

Preferred term Subject incidence: n(%)	Age ≤ 50		Age > 50	
	Placebo N=54	Buros N=52	Placebo N=12	Buros N=16
Any TEAE	49 (91)	49 (94)	12 (100)	15 (94)
Arthralgia	12 (22)	5 (10)	4 (33)	1 (6)
Nasopharyngitis	3 (6)	7 (14)	3 (25)	2 (13)
Back pain	4 (7)	8 (15)	2 (17)	2 (13)
Headache	4 (7)	4 (8)	1 (8)	4 (25)
Pain in extremity	7 (13)	2 (4)	3 (25)	3 (19)
Restless legs syndrome	3 (6)	3 (6)	1 (8)	5 (31)

Source: ISS Table 14.99.2.3.1.13.2

Analysis of AEs in white vs. non-white adult patients (82% and 18% of total respectively) is presented in ISS Table 14.2.3.1.4. No meaningful differences were apparent although the number of non-white patients in the trial is relatively small to provide any definitive conclusions.

8.3.7. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted for burosumab.

8.3.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

In the absence of a signal for increased malignancy, no specific study or monitoring was conducted to assess neoplasms. In clinical studies, malignancies were reported as AEs in 4 adult patients treated with burosumab:

- Study INT-001/002, patient # (b) (6), a 55 y/o female, was diagnosed with **breast cancer** on day 271, from ultrasound and biopsy of a longstanding R breast density
- Study CL203, patient # (b) (6), a 58 y/o male with family history of lung cancer but no tobacco history, was found to have a lung nodule on CXR at study screening, and biopsy 2 months later showed **lung adenocarcinoma**
- Study CL203, patient # (b) (6), a 58 y/o male, was incidentally found on renal ultrasound (conducted per study protocol) on day 673 to have a 12 cm sacral mass; biopsy revealed a **chordoma**
- Study CL203, patient # (b) (6), a 46 y/o female was diagnosed on study day 541 with **adenocarcinoma of the colon**. Subsequently based on genetic testing she was reported with an additional AE of hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome) and underwent TAH/BSO

In study CL303, one malignancy was reported, in a patient receiving placebo: patient # (b) (6), a 43 y/o female, was diagnosed on day 163 with invasive ductal breast cancer.

None of these reports appear to indicate a specific signal or trend that use of burosumab would increase the risk of any specific cancer or cancers.

Human Reproduction and Pregnancy

There are 3 reported cases of pregnancy during burosumab clinical trials, involving only early first trimester exposure:

- In study KRN23-INT-001, patient # (b) (6), a 32 y/o W/F, discontinued the study due to an AE of injection site urticaria following her third dose of burosumab (0.3 mg/kg) on day 57. She had a positive pregnancy test 10 weeks later. She delivered a healthy baby at term without complication.
- In study CL303, patient # (b) (6), a 26 y/o woman randomized to placebo, began open label burosumab on study day 170, had LMP on day 408, positive pregnancy test on day 453 and last dose of burosumab on day 423 (D/C per study protocol). The patient and fetus were doing well and EDC was in Dec. 2017.
- In study CL303, patient # (b) (6), a 35 y/o woman randomized to placebo, began open label burosumab on study day 169, had LMP on day 312, positive pregnancy test on day 345 and last dose of burosumab on day 336 (D/C per study protocol). The patient was planning to carry the pregnancy to term, with EDC in Dec. 2017.

There are no reports of burosumab exposure in lactating women. The Division of Pediatric and Maternal Health (DPMH) provided consultation regarding reproductive safety of burosumab and recommendations for labeling (see separate DPMH review). Regarding the study in pregnant monkeys as detailed above (section 5), DPMH and DBRUP agreed that the adverse findings are of uncertain relevance to humans with XLH, but that pregnant women receiving burosumab for XLH should be closely monitored with serum phosphorus levels throughout pregnancy to determine the need for any dose adjustment. Also recommended is a pregnancy surveillance substudy to be incorporated into the applicant's proposed Disease Monitoring Program (DMP) as a PMR. Because of the lack of data relevant to the effects of burosumab exposure on lactation, a postmarketing lactation study was also recommended as a PMR.

Pediatrics and Assessment of Effects on Growth

Phase 2 pediatric studies (CL201 in 5-12 year olds, CL205 in 1-4 year olds) are described in sections 8.1.1 and 8.1.3, respectively, of this review, including effects on growth which are important efficacy endpoints. There are no clinical studies which enrolled adolescents age 13-17 y/o; modeling was determined to be acceptable to provide an initial starting dose, and additional data on this subset of pediatric patients will be captured in the post-marketing surveillance study.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of toxicity due to overdose have been reported. Burosumab is not believed to have abuse or dependence potential.

In patients who received burosumab for 64 weeks in studies INT-001/002, then discontinued treatment for ~1.5-3.5 years before resuming burosumab in study CL203, serum phosphorus levels returned to baseline in the untreated interval. There was no evidence of withdrawal or rebound phenomena.

8.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Burosumab was granted conditional marketing authorization by the European Medicines Agency Committee for Medicinal Products for Human Use in December 2017, for treatment of XLH in the pediatric population. At this time, no postmarketing safety data are available.

Expectations on Safety in the Postmarket Setting

All patients in the burosumab studies had XLH and hypophosphatemia at baseline, did not use concomitant oral phosphate or active vitamin D analogs, and were monitored frequently for serum phosphorus levels. Potentially, off label use in patients without hypophosphatemia, with such concomitant medications and/or without close monitoring could entail a significant risk of serious ectopic mineralization. However with appropriate labeling, the risk of such an event is small. Only 2 patients age ≥ 65 years were enrolled in studies, and no adolescents (age 13-17 years), but safety in these groups is not expected to differ substantially from other age groups.

8.3.10. Integrated Assessment of Safety

The primary safety concern for the use of burosumab, in any age group, is the potential risk for dose-dependent hyperphosphatemia and ectopic mineralization. This is based on the pharmacologic effect of the drug in suppressing FGF23, and nonclinical studies in which elevated serum phosphorus (>8 mg/dL) was associated with mineralization in the kidney, cardiovascular tissues and other organs. Conventional therapy for XLH (phosphate/ calcitriol) is associated with a high prevalence of ectopic calcification (especially nephrocalcinosis and/or nephrolithiasis), most likely from treatment-related increases in urine phosphate and/or calcium. Burosumab does not appear to cause such increases, and may therefore offer improved safety compared to conventional therapy in this regard.

Ectopic mineralization was investigated with periodic renal ultrasound exams in the pivotal studies. In study CL201, nephrocalcinosis scores were unchanged from baseline in 36/52

patients (69%); decreased by 1 point in 3/52 patients (6%); and increased by 1 point in 13/52 patients (25%). In study CL303 as well, small increases (1 point) in nephrocalcinosis scores were more frequent than 1-point score decreases, however burosumab and placebo groups were similar in this regard. There were no score increases >1 point in these studies, and the 1-point increases were not associated with increased urinary calcium or decreased renal function. Although the risk of nephrocalcinosis with burosumab appears to be low, the planned postmarketing DMP study (section 12) should include renal ultrasound exams during long-term treatment.

Echocardiograms were also conducted routinely in patients ≥ 5 years old to monitor for possible cardiac or aortic calcification development. In study CL201, 2 patients had grade 1 ectopic mineralization at week 88 reported in the safety update, one of which was not apparent at week 112. In study CL303, there was no trend of worsening calcification, compared to baseline or to placebo.

Renal function is another potential safety issue with burosumab, primarily due to the risk of nephrocalcinosis. In addition, during this review cycle a concern was raised about potential antibody-dependent cellular cytotoxicity (ADCC) based on an *in vitro* assay, which would tend to affect α -klotho expressing tissues especially the renal tubules (see nonclinical review, section 5). Lab monitoring of renal function, including urine protein by dipstick UA in the pediatric and adult studies has not raised any concern, but monitoring of renal function should be included in the postmarketing DMP study.

Hyperphosphatemia is a potential concern with burosumab, mainly because if severe it may create a risk of severe ectopic mineralization, nephrocalcinosis and/or renal failure. Serum phosphorus levels were closely monitored in all studies. In the pediatric studies, levels were not allowed to remain above 4.5-5.0 mg/dL, which is well below the ULN; 3/65 patients underwent dose reductions for this purpose, and no patient had hyperphosphatemia. In the adult study CL303 through week 48, 17/134 patients had at least one level above 4.5 mg/dL, which is the ULN in adults, and 8 of these patients had dose reductions. All patients (pediatric and adult) treated with burosumab should undergo monitoring of serum phosphorus, at least during the first 3 months of treatment and following any change in dose.

Hyperparathyroidism is one of the major safety issues with conventional therapy for XLH, presumably caused by recurring spikes in serum phosphorus after each dose. Because of the different mechanism of action of burosumab, hyperparathyroidism is expected to occur much less frequently, if at all. In study CL201, many patients had elevated serum iPTH at baseline and/or during treatment, including two who also had high or high-normal serum calcium, suggesting autonomous parathyroid function. In study CL303, a 20 year old patient had fluctuating elevations of iPTH and calcium and eventually underwent removal of a parathyroid adenoma. Most likely, these cases represent sequelae of previous conventional therapy.

Overall, there was no evidence that burosumab increases PTH levels or causes hyperparathyroidism.

Spinal stenosis appears to be highly prevalent in adult patients with XLH, and in the combined adult study population (N=176), a total of 6 patients had undergone spinal surgery that was related to spinal stenosis as of the safety update cutoff. Calcification of intraspinal ligaments (enthesopathy) appears to be one of the common mechanisms of this complication of XLH, and exacerbation by burosumab is unlikely but cannot be ruled out. This issue warrants inclusion as an adverse drug event in product labeling and also as an adverse event that should be captured in the post-marketing surveillance study.

Injection site reactions (ISRs) were reported in 58% of the pediatric patients, but were invariably mild and did not result in any discontinuations. ISRs were much less common in adults (12% in both burosumab and placebo groups in study CL303), but resulted in one discontinuation in study INT-001 for injection site urticaria. The most common injection site symptom was erythema, followed by pain and pruritis. The data did not seem to indicate that long-term use of burosumab would increase the risk of these reactions or that there were measures to prevent the occurrence of these reactions.

AEs of potential hypersensitivity, most commonly rash, were reported in 39% of pediatric patients and 12% of adult patients, with no burosumab/placebo imbalance in study CL303. There were 2 children who had recurrences of hypersensitivity events (1 urticaria, 1 swelling face) after a 1-2 year hiatus, and no discontinuations. One SAE of angioedema was reported in a 68 y/o woman, but was likely due to lisinopril and the patient is continuing burosumab.

Restless legs syndrome (RLS) was reported in 9% of all adult patients, including in the double blind phase of study CL303, 8 burosumab and 5 placebo patients. Several had a prior history of RLS. One patient discontinued in study INT-001/002 due to worsening RLS, but subsequently enrolled in study CL203 and had no more recurrences. RLS occurred more commonly in adult males and patients >50 y/o and did not appear to represent a concerning safety trend that would require additional data at the time of the review of the submitted dataset.

8.4. Summary and Conclusions

XLH is a chronic disease that leads to excess FGF23 and results in renal phosphate wasting. The disease is initially diagnosed in childhood with hypophosphatemia leading inadequate skeletal mineralization, growth delay and leg bowing. Burosumab therapy in children with XLH resulted in a substantial increase in serum phosphorus, and improvement in radiographic rickets scores and serum alkaline phosphatase, with no evidence of loss of effect over time. There was little effect shown on growth and skeletal deformities, which likely require longer follow-up for the demonstration of such effects. Because of the central role of rickets in the pathogenesis of bone disease in XLH, children are expected to derive clinically meaningful benefits from

treatment, especially when treatment is begun at a very young age. The applicant's proposed pediatric dosing scheme (starting dose 0.8 mg/kg Q2W with titration up to 2.0 mg/kg based on serum phosphorus) is supported by the data in the younger and older children.

In adults with XLH, skeletal abnormalities from childhood (skeletal deformities and resultant osteoarthritis) are not remediable with burosumab therapy. The primary manifestations are hypophosphatemia with pain and stiffness impairing physical function. Robust increases from baseline in serum phosphorus were demonstrated, with most patients achieving and maintaining levels in the normal range. The applicant's proposed adult burosumab dose of 1.0 mg/kg Q4W is well supported by these data. Clinical benefits are harder to establish in the adult (compared to pediatric) XLH population. Small declines in pain scores relative to placebo did not reach statistical significance because the origins of pain in this population are complex and pain related to factors such as osteoarthritis and deformities cannot be expected to respond to this drug and likely require long-term followup. Objective evidence of substantial reduction in osteomalacia, both indirect (radiographic pseudofractures or fractures) and direct (bone biopsy parameters) was demonstrated. Although the clinical significance of these measures is uncertain, it is reasonable to assume that patients would benefit from this improvement in bone health.

The primary safety concern for the use of burosumab, in any age group, is the potential risk for dose-dependent hyperphosphatemia and ectopic mineralization. This is based on the pharmacologic effect of the drug in suppressing FGF23, and nonclinical studies in which elevated serum phosphorus (>8 mg/dL) was associated with mineralization in the kidney, cardiovascular tissues and other organs. Conventional therapy for XLH (phosphate/ calcitriol) is associated with a high prevalence of ectopic calcification (especially nephrocalcinosis and/or nephrolithiasis), most likely from treatment-related increases in urine phosphate and/or calcium. Burosumab does not appear to cause such increases, and may therefore offer improved safety as compared to conventional therapy in this regard.

Limitations of the clinical data for burosumab include the lack of a control group in the pediatric studies; lack of bone biopsy data in the pediatric population; lack of dosing and efficacy data in the adolescent population. For the lack of control group in the pediatric studies, comparison data from the natural history study (study CL002) provide some evidence and support for the conclusions reached. While bone biopsy data in the pediatric population would be ideal, osteomalacia is essentially the same disorder in children as in adults, and the evidence of improvements in osteomalacia in the adult studies can reasonably be extrapolated to children. For dosing in adolescents, most of whom have open growth plates, the pediatric dosing should be used, including burosumab Q2W with dose guided by serum phosphorus levels. The pediatric and adult studies showed similar effects on phosphorus and other PD endpoints, and favorable effects on skeletal endpoints; therefore, it is reasonable to expect significant treatment benefit in adolescents.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was conducted for this application.

10. Maternal Health and Pediatrics

XLH is a disease that manifests in the pediatric population. Burosumab trials include pediatric studies. The Division of Maternal and Pediatric Health (DPMH) were consulted and have provided consultation on the data and labeling for pediatrics. DPMH agreed that extrapolation of the pediatric and adult data to adolescents is appropriate. DPMH also recommended labeling changes to Section 8.4 Pediatric use of product labeling, which have been implemented.

DPMH has also recommended a pregnancy surveillance substudy, to be incorporated into the proposed XLH-DMP study as a PMR (section 12.1). Because of the lack of data relevant to the effects of burosumab exposure on lactation, a postmarketing lactation study was also recommended as a PMR.

Please see the separate consults in DARRTS for further details.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The applicant's proposed Prescribing Information, submitted with the 120-day Safety Update on 12/15/17, was reviewed. The following significant revisions are recommended:

- 4 CONTRAINDICATIONS

Comment: The applicant proposes a contraindication for (b) (4)

[REDACTED]

Therefore, the evidence does not support this contraindication.

- 5 WARNINGS AND PRECAUTIONS: W&P 5.2 Hyperphosphatemia
- *Comment:* The proposed language states that dose interruption or reduction may be required based on phosphorus levels, but does not state the actual risk involved. A statement should be added indicating that increased serum phosphorus may be associated with an increased risk of nephrocalcinosis.

- 6 ADVERSE REACTIONS:
Comment: In section 6.1, pediatric and adult adverse reactions should be discussed separately; vomiting and pyrexia should be added to the table of common reactions in pediatric patients; and exacerbation of spinal stenosis should be added to the reported reactions in adult patients.
- 8 USE IN SPECIFIC POPULATIONS:
Comment: Extensive changes needed in pregnancy, lactation, pediatric use subsections, including addition of a statement that serum phosphorus levels should be monitored throughout pregnancy. Subsection 8.5 Geriatric use needs re-writing to conform to regulations.
- 10 OVERDOSAGE:
Comment: Needs to be re-written to conform to regulations.
- 12 CLINICAL PHARMACOLOGY
Comment: Extensive changes needed, see review section 6.
- 13 NONCLINICAL TOXICOLOGY
Comment: Extensive changes needed, see review section 5.
- 14 CLINICAL STUDIES:
Comment: (b) (4)
Because of the importance of phosphorus to prescribers, serum phosphorus and TmP/GFR data should be presented first, before radiographic and growth data. Adult section (14.2) should also include data about mean changes in serum phosphorus and in TmP/GFR. As per recommendations of COA consultants, (b) (4) should be removed. Data on analgesic use, especially opioids, may be of use to prescribers and should be added. In the section on bone histomorphometry, additional data on osteoid thickness and mineralization lag time should be added to the proposed data on osteoid volume.

11.2. Carton and Container Labeling

The Division of Medication Error and Prevention has worked with the applicant on the carton and container labeling. Agreement has been reached and there are no outstanding issues from the medication error perspective. Please see the separate consults in DARRTS for further details.

11. Risk Evaluation and Mitigation Strategies (REMS)

DRISK, DBRUP and the applicant are in agreement that the potential risks of burosumab can be adequately managed in the postmarket setting through product labeling alone, and that a REMS is not necessary to ensure that the drug's benefits will outweigh the risks.

Please see the separate consult from the Division of Risk Management (*DRISK*) in DARRTS for complete details.

12. Postmarketing Requirements and Commitments

XLH is a chronic disease which may require lifelong treatment with burosumab beginning in childhood. Assessment of long term safety outcomes will be important for burosumab use in treatment of XLH. The safety endpoints of concern include nephrocalcinosis, the evaluation of renal function with assessments including both serum creatinine and urine protein quantitation because of the potential for renal tubule toxicity, and spinal stenosis surgeries.

In pre-submission meetings, the applicant indicated their plans for a postmarketing Disease Monitoring Program (XLH-DMP, also designated as study UX023-CL401) to gather additional long-term pediatric and adult safety and efficacy data for burosumab. According to the final protocol submitted on 12/1/17, this will be a 10-year study, (b) (6)

[Redacted]

[Redacted]

[Redacted]

[REDACTED] (b) (6)

[REDACTED]

[REDACTED]

Reviewer Comments:

This should be made a PMR study in order to resolve uncertainties about long-term efficacy and safety of burosumab in children and adults. In general the study design is appropriate. The protocol should provide more detail about the method to be used for assessment of nephrocalcinosis, [REDACTED] (b) (4)

[REDACTED] In addition, the safety objectives should include the evaluation of renal function, and assessments should include not only serum creatinine but urine protein quantitation because of the potential for renal tubule toxicity.

The following PMRs were recommended by the review team. These PMRs were discussed with the applicant and milestones for these studies have been agreed to by the applicant:

12.1. Postmarketing Requirements

12.1.1. Post-approval Surveillance Study

A post-approval surveillance program with safety objectives of evaluating the potential association between burosumab treatment and the risks of nephrocalcinosis, renal failure, and spinal stenosis. Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. This program will be incorporated into the X-linked Hypophosphatemia Disease Monitoring Program (study UX023-CL401) that collects information on the disease for up to 10 years. Safety data collection will begin within 90 days of protocol agreement. After marketing starts, submit progress reports to the FDA at six months, one year, and annually thereafter, with an evaluation of the effectiveness of meeting the surveillance program’s safety objectives. Collect surveillance data from a minimum of 500 subjects, 200 of whom will be pediatric patients, and approximately two-thirds will be treated with burosumab.

Proposed Timeline:

8/2018	Final Protocol Submission
2/2019	6 Month Progress Report
4/2019	Annual Report Submission, and annually thereafter
12/2028	Study Completion
8/2029	Final Study Report Submission

12.1. 2. Lactation SubStudy of the Post-approval Surveillance Study

In XLH patients enrolled in the prospective, longitudinal, surveillance study, perform a lactation sub-study in lactating women who have received therapeutic doses of burosumab using a validated assay to assess concentrations of burosumab in breast milk, the effects on milk composition (to include calcium and phosphorus levels), and the effects on the breastfed infant

Proposed Timeline (same as the postapproval surveillance study)

8/2018	Final Protocol Submission
12/2028	Study Completion
8/2029	Final Study Report Submission

12.1.3. An Immunogenicity Study

Conduct a study to reanalyze banked immunogenicity serum samples from XLH clinical trials including Study UX023-CL205, Study UX023-CL201, and Study UX023-CL303 to determine the presence of anti-drug antibodies (ADA) using a validated ADA assay with improved drug tolerance. Characterize the neutralizing activity of ADA for samples tested positive for ADA.

Evaluate the impact of immunogenicity on pharmacokinetics, efficacy and safety in subjects with XLH based on the ADA data generated with the newly validated assay.

Proposed Timeline:

12/2018:	Reanalysis of ADA and neutralizing antibody (Nab) data (including titer and incidence)
6/2019	Report of Immunogenicity impact assessment (studies CL205, CL201 and CL303)

12.2. Postmarketing Commitments

The following postmarketing commitment related to characterizing the master cell bank and evaluate the effector function with accompanying milestones have been agreed to by the applicant.

12.2.1. Characterization of the burosumab master cell bank

Conduct studies to further characterize the burosumab master cell bank (MCB) and to support the monoclonality of the MCB.

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Proposed Timelines:

12/2018: Final Protocol Submission
6/2020: Final Report Submission

12.2.2. Antibody Dependent Cellular Toxicity

Conduct studies to evaluate effector functions (i.e., antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity) of burosumab. The final Post Marketing Commitment report should be submitted based on the outcome of the studies per 21 CFR 601.12.

Proposed Timelines:

12/2018: Final Protocol Submission
12/2019: Final Report Submission

13. Appendices

13.1. References

Carpenter TO et al, A clinician's guide to X-linked hypophosphatemia, *J Bone Miner Res* (2011), 26: 1381-1388

Linglart A et al, Therapeutic management of hypophosphatemic rickets from infancy to adulthood, *Endocr Connect* (2014), 3: R13-R30

Thacher T et al, Radiographic Scoring Method for the Assessment of the Severity of Nutritional Rickets, *J Trop Pediatr* (2000), 46: pp. 132-139

Shore RM and Chesney RW, Rickets: Part II, *Pediatr Radiol* (2013), 43: pp. 152-172

13.2. Financial Disclosure

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The covered clinical studies, as defined by 21 CFR 54.2(e) were pediatric studies UX023-CL201, UX023-CL205 and UX023-CL002; and adult studies UX023-CL303 and UX023-CL304, which provided the primary evidence to establish effectiveness and safety of burosumab.

One investigator, [REDACTED] (b) (6) as a Principal Investigator, had disclosable financial arrangements with the applicant. As described in an attachment to [REDACTED] (b) (6) Financial Disclosure Form 3455, this consisted of approx. \$60K in payments related to the planning, protocol development and start-up for study CL201 during 2014, and approx. \$25K in general consulting fees from 2013 to date. Site # [REDACTED] (b) (6) recruited [REDACTED] (b) (6) of the 52 pediatric subjects in study CL201. A discussion of the steps taken in this study to minimize any bias was included. Although this study was open label, the key radiographic and PD assessments were made outside the clinical sites.

Reviewer Comments:

The disclosure of financial interests was adequate.

Covered Clinical Study (Name and/or Number): UX023-CL201

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>9 Principal Investigators, 63 Sub-investigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Multi-Disciplinary Review
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Covered Clinical Study (Name and/or Number): UX023-CL205

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>3</u> Principal Investigators, <u>11</u> Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Multi-Disciplinary Review
 BLA 761068
 (burosumab - twza)

Covered Clinical Study (Name and/or Number): UX023-CL002

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>4 Principal Investigators, 8 Sub-investigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Multi-Disciplinary Review
 BLA 761068
 (burosumab - twza)

Covered Clinical Study (Name and/or Number): UX023-CL303

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>25 Principal Investigators, 66 Sub-investigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

Multi-Disciplinary Review
 BLA 761068
 (burosumab - twza)

Covered Clinical Study (Name and/or Number): UX023-CL304

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>11</u> Principal Investigators, <u>27</u> Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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/s/

THERESA E KEHOE
04/11/2018

AUDREY L GASSMAN
04/11/2018

VICTOR CRENTSIL
04/11/2018

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA ID	C2017261
BLA #	761068
Referenced IND for NDA/BLA	N/A
Established Name/Trade Name	Burosumab
Applicant	Ultragenyx Pharmaceutical
Indication	X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older
Meeting Type/Deliverable	WRO
Applicant Letter Date/SDN #	August 17, 2017 / SDN 1
Date of Consult Request	August 24, 2017
Review Completion Date	January 17, 2018
Review Division	Division of Bone, Reproductive and Urologic Products
Clinical Reviewer/Clinical Team Leader(CTL)	Stephen Voss
Review Division PM	Samantha Bell
COA Reviewer	Yasmin Choudhry
COA TL/Secondary Reviewer	Selena Daniels
COA Associate Director	Elektra Papadopoulos
Instrument 1	Western Ontario and McMaster Universities Osteoarthritis Index
Instrument 2	Brief Pain Inventory (Item 3-Worst Pain)
COA Type 1 and Endpoint Concepts	Pain, stiffness, physical function
COA Type 2 and Endpoint Concepts	Pain
Intended Population	Adults and pediatric patients 1 years of age and older
Internal Meeting	MCR November 21, 2017; PDUFA April 17, 2018
Applicant Meeting/WRO	WRO

Please check all that apply:

- Rare Disease/Orphan Designation
- Pediatric

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761068

Burosumab

BPI-SF Item 3 (pain intensity); WOMAC (stiffness; physical function)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Bone, Reproductive and Urologic Products (DBRUP) regarding BLA 761068 (burosumab). The Applicant is in the BLA phase of their drug development program. The proposed indication is treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

The Applicant utilized the following patient-reported outcome (PRO) assessments as key secondary endpoints in the phase 3 clinical trial (UX023-CL303) in adult patients with X-linked hypophosphatemia:

- Brief Pain Inventory-Short Form (BPI-SF) –Item 3 (Worst Pain), which assesses severity and impact of pain on daily function. See Appendix A for a copy of the instrument.
- Western Ontario and McMaster Universities Arthritis Index (WOMAC), which assesses pain, stiffness, and physical function. See Appendix B for a copy of the instrument.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED] Therefore, this review is restricted to the PROs used in the adult study.

DBRUP requested COA input [REDACTED] (b) (4)
[REDACTED]

The review concludes that there are some potential measurement challenges with the instruments that might affect data interpretability. Below are some specific comments related to each instrument.

Brief Pain Inventory

Although the BPI-SF Item 3 appears fit-for-purpose in this clinical context, the Applicant was not able to demonstrate treatment effect on pain (i.e., statistically significant reduction in pain). Additional details may be needed to determine whether analgesic use supports the trend observed in pain reduction with treatment. We defer to Division whether an information request (IR) should be submitted to obtain further details on analgesic use.

We defer to the Division regarding [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

WOMAC

The WOMAC is not fit-for-purpose for this drug development program due to the following limitations:

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761068

Burosumab

BPI-SF Item 3 (pain intensity); WOMAC (stiffness; physical function)

- The intended use for the WOMAC is for patients with hip and knee osteoarthritis; the instrument's instructions on the case report form (CRF) ask patients to consider their "study joint" when responding to the instrument items.
- The WOMAC did not fully assess upper extremity joints. An XLH patient network described their condition as a "whole body issue," yet the WOMAC measured one element of their condition (i.e., lower extremity joints). However, it is acknowledged that the UX023-CL303 clinical trial was designed to assess the impact of XLH-related lower extremity deformity.
- Data interpretation is limited, because it is unknown whether patients understood and interpreted the instructions given by the site personnel ("think about the pain, stiffness, and difficulty with daily physical activities caused by XLH and not only arthritis") or defaulted to written instructions on the CRF.

Based on the Hochberg approach, the WOMAC stiffness domain demonstrated statistical significance. However, it is unclear whether the reduction in stiffness was clinically meaningful in the absence of interpretable anchor-based cumulative distribution function (CDF) plots. The Applicant was not able to demonstrate treatment effect on physical function. We defer to the Division (b) (4)

Future medical product development in XLH

For future clinical trials in this indication, we recommend the use of a fit-for-purpose instrument that can assess the "whole body" experience without attribution made to the "study joint." In addition to concepts of pain and stiffness, the following concepts should be measured as confirmed by an XLH patient network: mobility (e.g., range of motion), fatigue, and dental abscesses. For rare conditions, such as XLH, it will be important to include sensitive and age-appropriate outcome measures to quantify disease.

B. BACKGROUND

Materials reviewed:

- Applicant's submission (SDN 1) received August 17, 2017 (PRO Evidence Dossier)
- DBRUP consult request dated August 24, 2017
- COA Reviews: C2017117 IND 76488 Papadopoulos [Reference ID: 4104364]

Clinical Outcome Assessment Review

Yasmin Choudhry, M.D.

BLA 761068

Burosumab

BPI-SF Item 3 (pain intensity); WOMAC (stiffness; physical function)

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

The phase 3 clinical trial (UX023-CL303) population was adult (18-65 years) males or females with a diagnosis of X-linked hypophosphatemia (XLH) supported by classic clinical features of adult XLH (such as short stature or bowed legs) and at least ONE of the following at Screening:

- 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 (iFGF23) level > 30 pg/mL by Kainos assay
- Biochemical findings consistent with XLH at SV2 following overnight fasting (min. 8 hours): Serum phosphorus < 2.5 mg/dL (0.81 mmol/L); and ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR) of < 2.5 mg/dL.

1.2 Clinical Trial Design

Study UX023-CL303: A phase 3, placebo-controlled study to evaluate the safety and efficacy of burosumab in adult subjects with X-Linked Hypophosphatemia (XLH). The objectives of this study were to demonstrate an overall improvement in bone health and metabolism and a directional improvement within the clinical, patient-reported outcome (PRO) and health-related quality of life data.

1.3 Endpoint Hierarchy and Definition

The Applicant's endpoint model is presented below in Table 1.

Table 1. Endpoint Model

Concept	Claim	Endpoint
Primary Endpoint		
Serum phosphorus levels	Achievement of mean serum phosphorous levels above the lower limit of normal (LLN)	Serum phosphorous levels above the lower limit of normal (LLN: 2.5mg/dL [0.81 mmol/L]) at the mid-point of the dose interval (i.e., Weeks 2, 6, 10, 14, 18 and 22), as averaged across dose cycles between baseline and Week 24.
Key Secondary Endpoints		
Pain		(b) (4) Change from baseline to Week 24 in BPI-SF Q3 (Worst Pain) score, as averaged from daily diary scores recorded over 1 week and the study visit score.
Stiffness		Change from baseline to Week 24 in the Stiffness domain score of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC®)
Physical Function		Change from baseline to Week 24 in the Physical Functioning domain score of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC®)

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1.4 Labeling or promotional claim(s) based on the COA

The Applicant seeks the following COA-related labeling claims:



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2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The conceptual frameworks for the BPI-SF and WOMAC and are shown in Figures 1 and 2.

Figure 1. BPI-SF Conceptual Framework

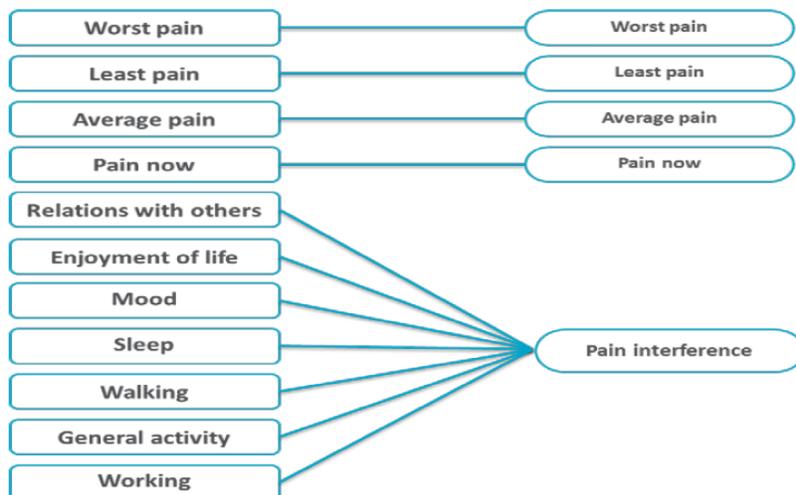
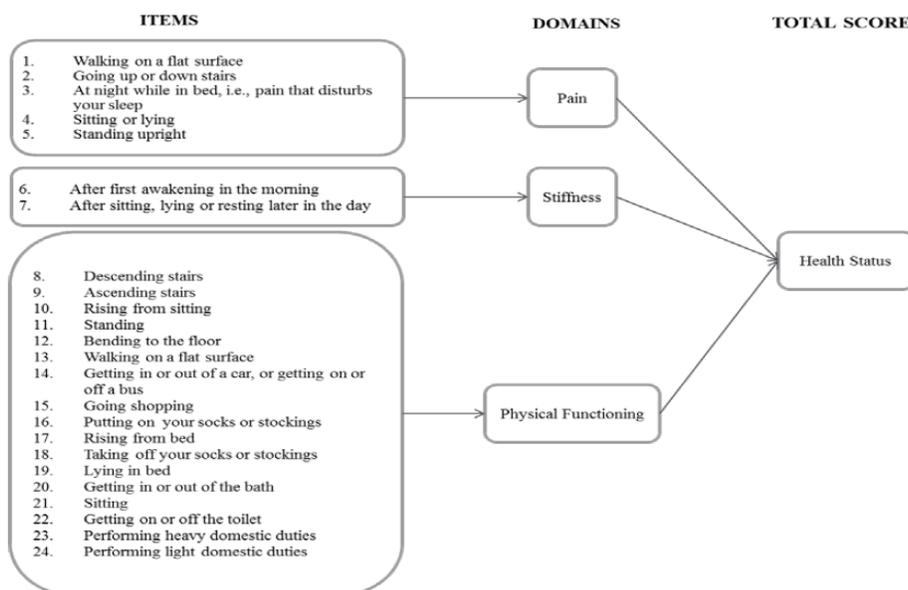


Figure 2. WOMAC Conceptual Framework



3 CLINICAL OUTCOME ASSESSMENT(S)

Brief Pain Inventory—Short Form (BPI-SF) – Item 3 (Worst Pain): See Appendix A.

The BPI-SF is a 9-item PRO that includes 9 items under the following domains:

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- Pain severity (4 items): Items ‘worst pain’, ‘average pain’, ‘least pain’ and ‘current pain’. The items are assessed on an 11-point numerical rating scale (NRS) ranging from 0=No pain to 10=Pain as bad as you can imagine.
- Pain interference (7 items): Walking ability, sleep, mood, enjoyment of life, general activity, normal work, and relationships with other people. The items are assessed on an 11-point NRS ranging from 0=Does not interfere to 10=Completely interferes.

While the entire BPI-SF was completed by patients, for the purpose of this review, the focus is on the BPI-SF Worst Pain item as a key secondary endpoint [REDACTED] (b) (4)

Western Ontario and McMaster Universities Arthritis Index (WOMAC): See Appendix B. The WOMAC version LK3.1 (utilized in the adult Phase 3 trial (UX023-CL303)) is a 24 item PRO instrument designed to assess osteoarthritis-related signs, symptoms, and impacts. The WOMAC is comprised of the following domains:

- Pain (5 items)
- Stiffness (2 items)
- Physical functioning (17 items)

The recall period is *the last 48 hours*. The response options are: none (0), mild (1), moderate (2), severe (3), and extreme (4). The instructions state the following:

Stiffness: *Think about the stiffness you felt in your [study joint] caused by arthritis during the last 48 hours*

Physical functioning: *Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your [study joint]*

A pen and paper mode of the WOMAC was administered in Study UX023-CL303 at Baseline (Week 0) and Weeks 12, 24, 36, 48, 72 and 96.

Reviewer comment: This reviewer believes that the WOMAC’s appropriateness for this context of use is questionable. The WOMAC was developed for use in clinical trials in patients with hip and/or knee osteoarthritis and the instruments instructions specify that patients should consider a “target joint” when responding to the instrument items. The instructions ask patients to focus on a certain joint. However, it is unclear which joint(s) patients in this clinical trial were thinking about when responding to the stiffness and physical function items in this instrument. It appears that patients with XLH can have multiple joint involvement including spine and joints of upper extremities.

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4 SCORING ALGORITHM

BPI-SF Item 3 (Worst Pain)

Scores for Item 3 range from 0 to 10, where 0 represents no pain and 10 the worst imaginable pain (“pain as bad as you can imagine”).

WOMAC version LK3.1

Scores are normalized to a 0-100 metric representing the percent of the maximum score, where 0 represents the best health state and 100 the worst. Higher scores indicate worse pain, stiffness, and physical functioning. All items are weighted equally in the domain scores and the total summary score. The domain scores and total score are calculated by summing the individual item scores in each domain.

5 CONTENT VALIDITY

BPI-SF Item 3 (Worst Pain)

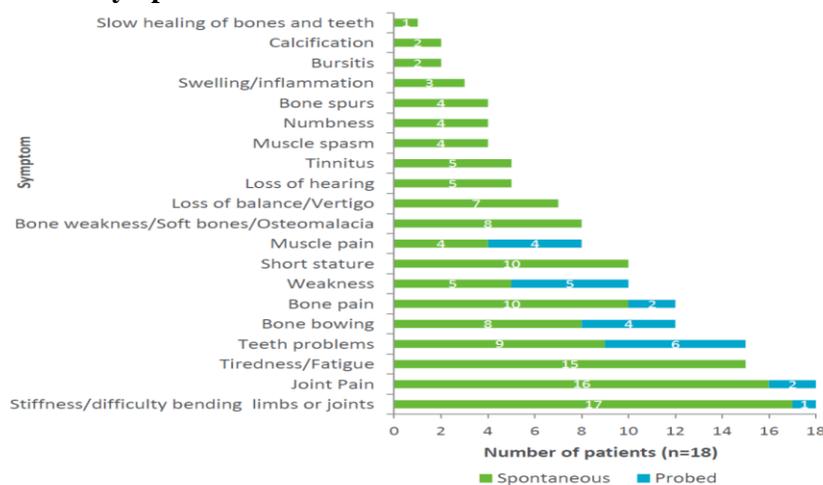
The Applicant did not conduct any qualitative work with the BPI-SF in the target population. However, pain appears to be a relevant concept for this population. The BPI-SF has been previously accepted as adequate for pain assessment.

WOMAC version LK3.1

Concept elicitation interviews:

Qualitative interviews were conducted (Study UX7181B) in 18 adult patients (18-65 years of age) with XLH to evaluate content validity of the BPI-SF and WOMAC. Patients were excluded if they were currently enrolled in Ultragenyx study UX023-CL203. The mean age of patients was 42 years (range 20 to 60 years) and the majority of the patients were female (83%, n=15). Figures 3 and 4 list the elicited XLH symptoms and impacts from XLH patients.

Figure 3. Elicited XLH Symptoms



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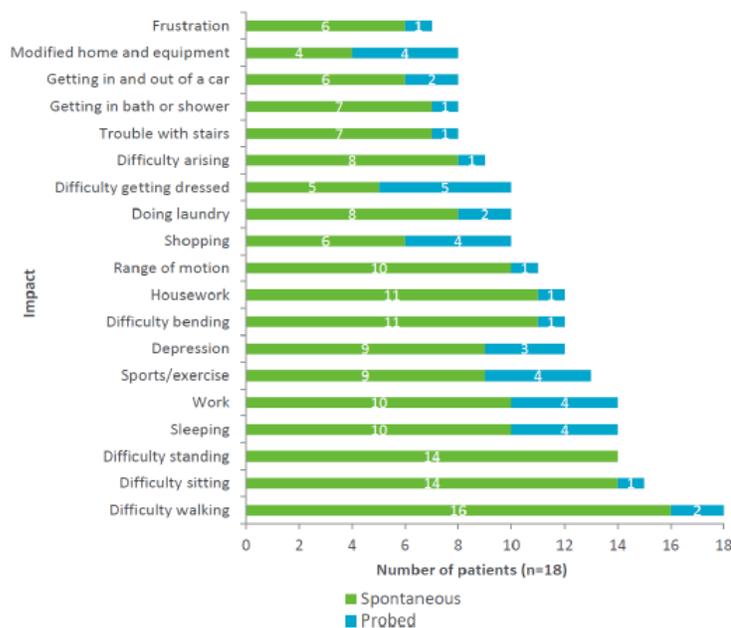
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Reviewer comments: The figure 3 shows that the most commonly reported symptoms were stiffness (18/18), joint pain (18/18), tiredness/fatigue (15/18), teeth problems (15/18), bone bowing (12/18) and bone pain (12/18).

Figure 4. Elicited XLH Impacts



Reviewer comment: See COA Review C2017117 Papadopoulos [Reference ID: 4104364] for details on content validity.

In summary, the Applicant identified the most important and commonly reported symptoms and impacts of XLH. According to the briefing package, saturation was achieved. The most commonly reported symptoms were stiffness of joints (18/18), joint pain 18/18), and fatigue (15/18); and the most commonly reported impacts were difficulty walking (18/18), difficulty sitting (15/18), difficulty standing (14/18).

Patients with XLH also have involvement of other joints (e.g., cervical spine, upper extremities). It is unclear why the results of content validity do not capture other joint involvement. See Figures 6, 7 and 8 under Section C6: Other Measurement Properties of this review.

Cognitive Interviews:

For the WOMAC Stiffness Domain, patients generally found the stiffness items relevant (16/18 for stiffness with walking and 15/18 for stiffness after sitting or lying down). It is unclear whether the patients were debriefed on the WOMAC's instructions particularly, the part of the

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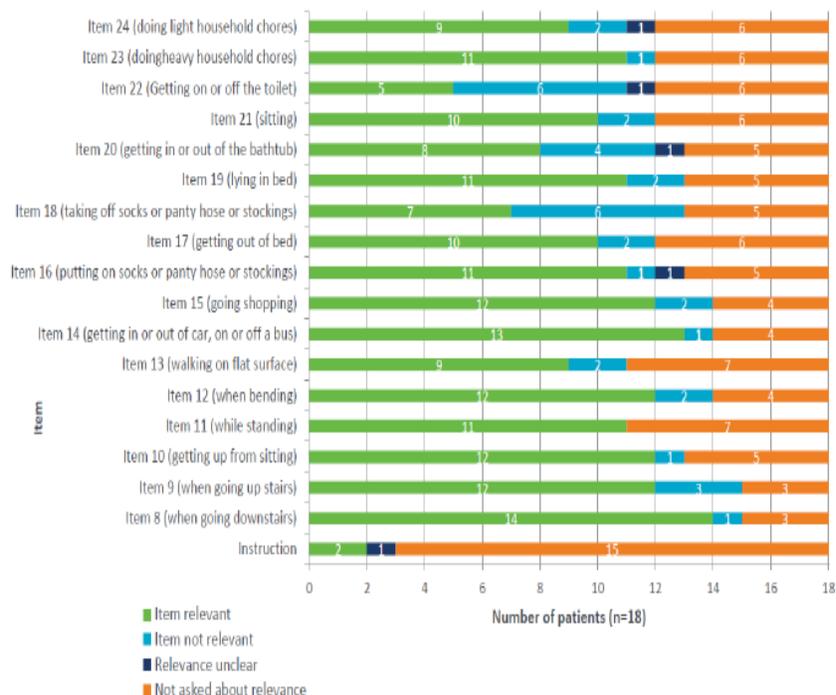
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instructions that asks patients to focus on their “study joint” when answering the question. For item relevance of the physical functioning domain see the figure 5 below.

Figure 5. Item relevance of the WOMAC Physical Functioning domain



The majority of patients who were asked about relevance of the items found them to be relevant with the exception of item 22 (getting on or off the toilet). In addition, item 18 was not relevant in 6 of 13 patients who were asked. Thirteen patients were asked about the ease of selecting a response on the response scale; all of whom confirmed they found it easy to select a response on the scale. All of the items were well-understood by patients.

Reviewer comments:

In response to the Information Request (IR) dated November 30, 2017, the Applicant stated that subjects were instructed to consider the impact of XLH on “all lower extremity joints, including hips, knees, ankles, and feet” when responding to the items. They indicated that the instructions were modified and tested in patients. However, this reviewer was not able to locate this information in the CRFs (Study UX023-CL 303).

Submission (SDN 33) received January 9, 2018 (in response to IR dated December 28, 2017), the Applicant stated that due to copyright restrictions, the WOMAC instructions could not be modified. However, the site staff were trained to instruct the patients at the time of the

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WOMAC administration to consider all lower extremity joints including hips, knees, ankles and feet; and to think about the pain/stiffness/difficulty with daily physical activities caused by XLH and not only arthritis. Additionally, the WOMAC instructions were debriefed with patients during the interviews. Patients were asked to refer to their ‘study bone/joint’ and to think about their ‘condition’ (rather than arthritis as stated in the WOMAC® instructions) when responding. The Applicant concluded that the majority of participants understood the instructions well, and were able to think about their XLH when responding to the items.

This reviewer believes that patients cannot (and should not be expected to) reliably differentiate whether their symptoms/physical limitations are due to XLH or arthritis. The addition of “study bone/joint” may have been even more confusing to patients as in XLH, more than one bone/joints may be affected.

Item response distribution and floor and ceiling effects:

The Applicant indicated that no concerns were identified in levels of the floor and ceiling effects for either study in either instrument; and that the findings suggested that the items have the potential to be responsive to both worsening and improvements in scores and should be able to discriminate patients of differing severity levels. Examination of the item response distributions again did not suggest that there should be cause for concern.

Reviewer’s comments: An IR was generated on November 30, 2017 asking the Applicant to provide the following additional data for the WOMAC using UX023-CL303 trial data with both raw and transformed scores

- *Item and Domain-level analyses*
- *Descriptive statistics (N, mean, standard deviation [SD], minimum, maximum, and % missing) for the WOMAC items, domain scores and total score by study visit*
- *Baseline WOMAC item scores, domain scores and total score along with item distributions by response categories, and floor and ceiling effects for each item.*

Based on the data provided, no ceiling effects were found and floor effects were found in only 5 items (4 items out of 17 items in physical function domain, 1 item out of 5 items in pain domain and 0 items in stiffness domain). The floor effects found were found in under 30% of the subjects. The applicant interpreted the floor and ceiling effects using the rule of: > 20% (100/number of response options) in the top or bottom response category are considered substantial. The floor and ceiling effects are shown in the Table 3.

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Table 3. Response distribution for the WOMAC items: Study UXO23-CL001 (n=201)

Item	None	Mild	Moderate	Severe	Extreme
1. How much pain you had when walking on a flat surface?	31 (15.9%)	56 (27.9%)	78 (38.8%)	29 (14.4%)	6 (3.0%)
2. ...when going up or down stairs	19 (9.5%)	41 (20.4%)	63 (31.3%)	61 (30.3%)	17 (8.5%)
3. ...while in bed? (that is – pain that disturbs your sleeps)	70 (34.8%)	50 (24.9%)	51 (25.4%)	26 (12.9%)	4 (2.0%)
4. ...while sitting or lying down?	73 (36.3%)	65 (32.3%)	41 (20.4%)	21 (10.4%)	1 (0.5%)
5. ...while standing?	27 (13.4%)	55 (27.4%)	69 (34.3%)	37 (18.4%)	13 (6.5%)
6. How severe your stiffness has been after you first woke up in the morning?	17 (8.5%)	56 (27.9%)	54 (26.9%)	60 (29.9%)	14 (7.0%)
7. ...after sitting or lying down or while resting later in the day?	23 (11.4%)	38 (18.9%)	72 (35.8%)	60 (29.9%)	8 (4.0%)
8. How much difficulty have you had when going down the stairs?	26 (12.9%)	47 (23.4%)	60 (29.9%)	44 (21.9%)	24 (11.9%)
9. ...when going up the stairs?	26 (12.9%)	55 (27.4%)	69 (34.3%)	30 (14.9%)	21 (10.4%)
10. ...when getting up from a sitting position?	34 (16.9%)	43 (21.4%)	75 (37.3%)	38 (18.9%)	11 (5.5%)
11. ...while standing?	29 (14.4%)	58 (28.9%)	67 (33.3%)	38 (18.9%)	9 (4.5%)
12. ...when bending on the floor?	46 (22.9%)	42 (20.9%)	39 (19.4%)	48 (23.9%)	26 (12.9%)
13. ...when walking on a flat surface?	35 (17.4%)	64 (31.8%)	70 (34.8%)	24 (11.9%)	8 (4.0%)
14. ...getting into or out of a car, or getting on a bus?	37 (18.4%)	47 (23.4%)	57 (28.4%)	48 (23.9%)	12 (6.0%)
15. ...while going shopping?	38 (18.9%)	43 (21.4%)	58 (28.9%)	43 (21.4%)	19 (9.5%)
16. ...when putting on your socks or panty hose or stockings?	60 (29.9%)	45 (22.4%)	46 (22.9%)	29 (14.4%)	21 (10.4%)
17. ...when getting out of bed?	40 (19.9%)	53 (26.4%)	62 (30.8%)	31 (15.4%)	15 (7.5%)
18. ...when taking off your socks or panty hose or stockings?	63 (31.3%)	51 (25.4%)	49 (24.4%)	24 (11.9%)	14 (7.0%)
19. ...while lying in bed?	79 (39.3%)	61 (30.3%)	40 (19.9%)	16 (8.0%)	5 (2.5%)
20. ...when getting in or out of the bathtub?	57 (28.4%)	45 (22.4%)	52 (25.9%)	25 (12.4%)	22 (10.9%)
21. ...while sitting?	75 (37.3%)	66 (32.8%)	44 (21.9%)	12 (6.0%)	4 (2.0%)
22. ...when getting on or off the toilet?	74 (36.8%)	59 (29.4%)	42 (20.9%)	16 (8.0%)	10 (5.0%)
23. ...while doing heavy household chores?	25 (12.4%)	35 (17.4%)	46 (22.9%)	53 (26.4%)	42 (20.9%)
24. ...while doing light household chores?	44 (21.9%)	61 (30.3%)	54 (26.9%)	34 (16.9%)	8 (4.0%)

Floor effect (>20%)

Ceiling effect (>20%)

Reviewer comments: While the Applicant identified the symptoms that were most relevant to this patient population, there are issues with content validity. As noted above, the instructions of the WOMAC are not fit-for-purpose. If the instructions of the questionnaire are not well understood by patients, it is likely that their responses to items may be inconsistent. Additionally, it is not clear why patients did not mention involvement or limitations with other areas of the body (e.g., upper extremities, spine). The patient transcripts were not provided in the SD 177 and therefore were not reviewed. Of note, the White Paper: Rickets XLH, March 3, 2016 (Type B Meeting Briefing Document SDN 177) also describes bending of the spine, knobby projections of the ribcage, weak and toneless muscles, osteoarthritis of knees, ankles and hips, and mineralization of tendons/ligaments (enthesopathy), and fragility of bones leading to pseudo-fractures.

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6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant evaluated the other measurement properties of the BPI-SF, WOMAC Physical Functioning and Stiffness domains using data from the online burden of illness study (UX023-CL001) and an open-label extension study (UX023-CL203). For details of the results see Appendix F of the Evidence Dossier.

Reviewer comment: Because of significant issues with content validity of the WOMAC, we did not conduct an in-depth review of the measurement properties. A brief summary of the results is included below. Of note, the evidence dossier cautions the reader that sample size for these analyses was very small (N=20), therefore, all results should be interpreted with caution. While sample size of study UX023-CL001 was much larger (N=201) than open-label extension study, the results of this study should also be interpreted with caution as the sample for study UX023-CL001 is much broader than the clinical trial sample and not necessarily representative of trial populations.

Study UX023-CL001: Demographics and Descriptive statistics:

Figure 6. Patients who had experienced joint pain in the last year by locations of joint

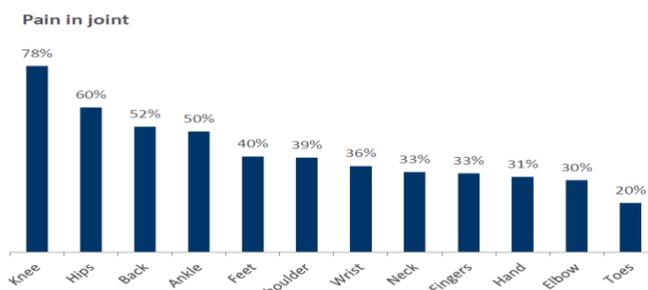
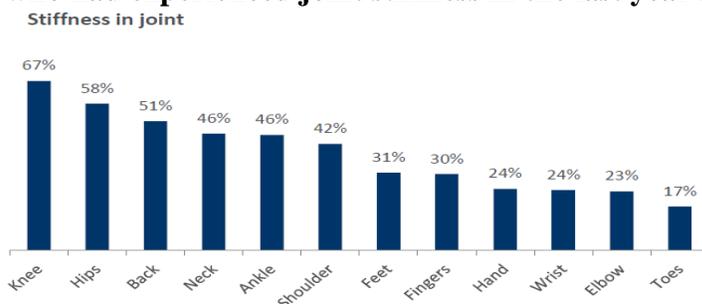


Figure 7. Patients who had experienced joint stiffness in the last year by location of joint



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Figure 8. Patients who had experienced bone pain in the last year by location of bone

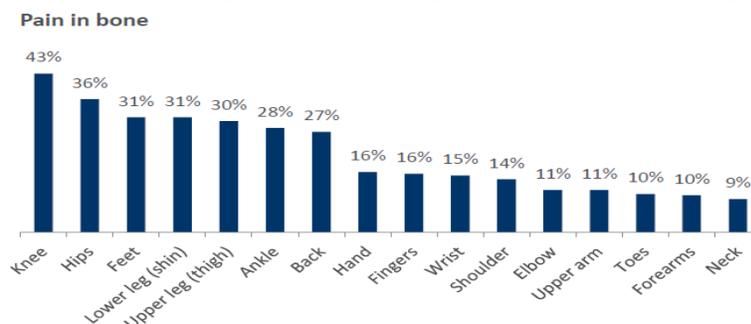


Table 2. Descriptive statistics of the WOMAC domain and total scores in UX023-CL001 (n=201) and UX023-CL203 (n=20) at baseline.

Domain	Online study (UX023-CL001)			Open-label extension study (UX023-CL203) at baseline		
	Mean (SD)	Median	Min-Max	Mean (SD)	Median	Min-Max
Pain score	38.7 (22.6)	40	0.0-100.0	40 (19.3)	42.5	5.0-7.0
Stiffness score	49.4 (24.9)	50	0.0-100.0	49.4 (14.3)	50	25.0-75.0
Physical functioning score	40.1 (24.7)	39.7	0.0-100.0	40.5 (20.3)	41.2	7.4-76.5
Total score	40.6 (23.0)	41.7	0.0-94.8	41.1 (18.5)	18.5	8.3-70.8

A summary of the reliability/validity results from the two studies: Study UX023-CL001 (online study; n=201); and Study UX023-CL203 (pooled data from the open-label extension study; n=) is as follows:

Reviewer comments: *The Applicant's report (reviewed by (b) (4) cautions that given the small sample sizes used in the open-label study, the data from the open label study should be interpreted with caution.*

Reliability: WOMAC and BPI-SF

Test-retest reliability: Evidence that scores are stable over time when no change has occurred in the patient's disease status (Intra-Class Correlation (ICC) coefficients).

- Study UX023-CL001 (Online study, n=201): Test-retest reliability was not evaluated as the WOMAC and BPI-SF were only administered at a single time point.

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- Study UX023-CL203 (Open-label study, n=20): An exploratory post-hoc analysis was conducted (in which the whole sample (n=20) was defined as stable¹), provided moderate to strong test-retest reliability for the majority of BPI-SF and WOMAC scale.

Internal consistency reliability: The extent to which items comprising a scale measure the same construct (i.e., homogeneity of the scale).

Cronbach's alpha was calculated using data from Study UX023-CL203. The Cronbach's alpha for WOMAC Physical function domain was high (0.9). Cronbach's alpha for WOMAC Physical function domain was high (0.9). Results for the WOMAC Stiffness domain were not provided.

Construct Validity:

Confirmatory Factor Analysis (CFA): Items were expected to load on their hypothesized domain with a standardized factor loading of > 0.40.

CFA was conducted on the WOMAC using data collected at baseline in UX023-CL001 only, to evaluate the extent to which the published conceptual framework was supported by the data from this XLH population. The factor loadings were all substantially higher than the 0.40 threshold (range: 0.815-0.934), supporting (moderate) the item-score structure.

Item Convergent Validity and Item Discriminant Validity: Evidence that relationships among items, domains, and concepts conform to a priori hypotheses concerning logical relationships that should exist with other instruments or characteristics of patients and patient groups.

- Study UX023-CL001: Moderate to high correlations were seen between the WOMAC domains of interest and the SF-36 physical functioning domain.
- Study UX023-CL203: Low correlations were seen between the WOMAC Physical function and Stiffness domains (-0.165 and -0.38 respectively) and SF-36 domains (Physical Functioning, Role Physical, and Bodily Pain) at week 24.

Known-groups validity: Evidence that the instrument can differentiate between clinically distinct groups (i.e., known groups validity). For UX023-CL001 and Study UX023-CL203, severity groups were defined in two ways: (1) pain medication use and (2) pain severity.

For the pain medication approach, the following categories were used to create severity groups: Uses pain medication at least once a week; uses narcotic pain medication at least once a week; uses narcotic pain medication at least once a week; current use of a walking device; experiences

¹ Stability defined as: Subjects who had a change in 6MWT of +/-<20 meters between BL & week 24; and a total score change of +/-<0.8 seconds for the TUG between BL & week 24.

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severe vs mild/moderate pain severity. The Applicant's results of the known groups validity for pain intensity are shown in table 3.

Reviewer comments: *We do not agree with the Applicant's severity groups as these are not clinically defined groups (e.g., mild, moderate and severe). Use of pain medication can be influenced by factors other than pain (such as pain tolerance).*

Additionally, the open-label extension study sample size and difference in numbers between groups was small. Statistically significant results were not seen with this study in these severity groups.

Table 3. Construct validity of BPI-SF/WOMAC using known groups method for the UX023-CL001 (n=201) and UX023-CL203 (n=20) by pain severity.

Scale	Online survey (UX023-CL001, n=201)			Open-label study (UX023-CL203, n=20)		
	Severe pain severity (>=6) Mean (SD) n=96	Mild/moderate pain severity (<6) Mean (SD) n=105	p-value*	Severe pain severity (>=6) Mean (SD) n=14	Mild/moderate pain severity (<6) Mean (SD) n=6	p-value*
BPI-SF Least pain score (0-10)	3.2 (1.7)	0.8 (1.0)	<0.001	3.1 (2.3)	0.8 (0.8)	0.003
BPI-SF Average pain score (0-10)	5.4 (1.3)	2.8 (1.7)	<0.001	5.0 (1.5)	2.7 (0.8)	0.002
BPI-SF Pain now score (0-10)	5.2 (2.1)	1.6 (1.5)	<0.001	4.4 (1.3)	1.7 (0.8)	<0.001
BPI-SF Pain interference score (0-10)	6.2 (2.3)	2.2 (2.0)	<0.001	4.6 (1.8)	3.4 (1.8)	0.176
WOMAC® Pain score (0-100)	54.1 (15.9)	24.7 (18.1)	<0.001	49.3 (12.4)	18.3 (14.4)	<0.001
WOMAC® Stiffness score (0-100)	64.3 (18.0)	35.7 (22.4)	<0.001	51.8 (13.7)	43.8 (15.3)	0.261
WOMAC® Physical functioning score (0-100)	55.8 (17.9)	25.7 (21.1)	<0.001	48.6 (15.8)	21.6 (17.4)	0.003
WOMAC® Total score (0-100)	56.2 (15.9)	26.3 (18.9)	<0.001	49.0 (13.4)	22.7 (15.7)	0.001

Variable "worst pain score" was not included in the analysis in Table 29 because n=1 in one group.

Reviewer comments: *While, the mean scores for all BPI-SF and WOMAC scale scores taken in the online survey (UX023-CL001) were significantly higher in the group that reported severe pain intensity than the group that reported mild/moderate pain intensity, results from the open-label study (UX023-CL203) showed that three BPI-SF scale scores ("least pain score", "average pain score", "pain now score"), and three WOMAC scale scores ("pain score", "physical functioning", "total score") were significantly different by pain severity.*

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However, the BFI-SF “pain interference score” and WOMAC “stiffness score” were not significantly different.

These results should also be interpreted with caution due to the small sample size and differences in numbers per group (6 vs 14). Additionally, the Applicant did not provide justification for the cutoffs for mild, moderate and severe pain.

Ability to detect change: Evidence that an instrument can identify differences in scores over time in individuals or groups who have changed with respect to the concept.

The Applicant conducted responsiveness analyses to determine the extent to which BPI-SF and WOMAC scores were able to detect changes in patients when their clinical status has improved between baseline and week 24, using the data from the open-label extension study only (UX023-CL203). Improved and not improved groups were based on a 6MWT and TUG test (Participants showing +/- >0.5SD change in each of these tests).

Reviewer comments: Since there were very limited numbers in the ‘improved’ group using both the 6MWT definition (n=3) and TUG definition (n=6), the Applicant chose not to present figures for this analysis as the sample did not allow inference to be drawn regarding ability to detect change.

7 INTERPRETATION OF SCORES

For BFI-SF Item 3 (worst pain) and WOMAC Physical Functioning and Stiffness domains, anchor- and distribution-based approaches were used to define the magnitude of change that can be considered meaningful. The Applicant concluded that the estimates for thresholds for meaningful change based on anchor- and distribution-based methods for the WOMAC were as follows:

- The BPI-SF Item 3 (worst pain) estimates (anchor-based, ½ SD, SEM) were in the range of 0.91-1.62, with a mean percentage change from baseline of -23.65%
- The WOMAC Stiffness domain ranged from 7.16-16.67; and the Physical functioning domain ranged from 4.10-13.6

Reviewer comments: The anchor-based estimates for these variables includes large standard deviations, most likely due to the small samples change between baseline and week 24 for stiffness (-16.67 (SD:21.48)) and physical functioning (13.63 (SD: 21.82)). The Applicant proposed to use the upper end of the range. The clinical meaningfulness of the proposed ranges is not known.

The Applicant provided cumulative distribution functions (CDF) curves based on change from baseline and percent change from baseline to Week 24 in mean BPI Worst Pain score, WOMAC

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Stiffness and Physical Function scores were plotted by treatment groups. See clinical study report for Study UXO23-CL303 (page 1216/2366).

The BPI Worst Pain responder analyses were based on the following definitions:

- Subjects with at least 15% decrease from baseline
- Subjects with at least 30% decrease from baseline

The current submission included the following minimum perceptible clinical improvement (MPCI) for the WOMAC domains based on published literature (the WOMAC User Guide (Bellamy 2012)): WOMAC Stiffness: 10.0 nu; and WOMAC Physical Functioning: 9.3 nu.

The Applicant concluded that the psychometric validation of the WOMAC in patients with XLH found similar MPCI values. For each of the WOMAC domains, responders were defined as subjects with a decrease from baseline greater than or equal to the corresponding MPCI.

Reviewer comments: The clinical meaningfulness of the MPCI proposed ranges is not known.

Of note, in Study UX023-CL303, the Patient Global Impression of Severity (PGI-S) / Patient Global Impression of Improvement (PGI-I) were also utilized. The 4-point PGI-S was administered at the Baseline visit; and the PGI-I (7-point categorical scale ranging from ‘very much better’ to ‘very much worse’) was administered at Weeks 12, 24, 36, and 48.

The Applicant was requested (IR dated November 30, 2017) to provide anchor-based CDF figures with the PGI-I. The Applicant responded (in SDN 23) that “they were unable to construct the requested plots for the WOMAC Stiffness, WOMAC Physical Function, and BPI Worst Pain score demonstrating a change from baseline in either patient global impression of improvement (PGI-I) scales as the PGI-S was only administered at baseline, while the PGI-I was administered at week 12 and week 24.” Despite this statement, the Applicant did provide CDF and PDF plots. Upon review, the CDF plots based on the 7 categories of the PGI-I (i.e., from very much better, much better, a little better, no change, a little worse, much worse, and very much worse) demonstrate most categories are overlapping except for the “much better” category. However, the distribution of patients across the categories is poor and there is a lack of precision in the estimate of the clinically meaningful threshold due to the small number of patients in the much better category. Therefore, the CDFs are difficult to interpret.

Based on the information reviewed, we believe that the thresholds for meaningful change in the instruments for this target population is unknown.

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8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The evidence dossier states that for all languages included in the clinical trial(s), a fully translated and linguistically validated version of the BPI-SF and WOMAC Version LK3.1 was used.

Reviewer comments: The BPI has been translated into dozens of languages, and it is widely used in both research and clinical settings. The BPI is available in two formats: the BPI short form, which is used for clinical trials and is the version used for the foreign-language translations.

Based on the publications cited in the user guide it appears the following languages are available: Spanish; Taiwanese; Russian; Italian; Norwegian; Greek; Canadian French; French; German; and Japanese Chinese Korean.

The user guide does not specify what process was used to translate the BPI-SF.

The WOMAC Version LK3.1 has been translated and linguistically validated in French-Canadian. The Phase 3 clinical trial (UX023-CL303) was conducted at sites in countries including the USA, UK, Ireland, Japan (Japanese), Canada (French Canadian), France (French), Denmark (Danish), Italy (Italian) and Korea (Korean). It is unclear whether the WOMAC was appropriately translated into the relevant languages (Japanese, Danish, Korean, Italian etc.)

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

10 REVIEW USER MANUAL

A user manual for the BPI-SF and WOMAC were not included in the evidence dossier.

11 KEY REFERENCES FOR COA

Not applicable.

12 APPENDICES

Appendix A: BPI-SF

Appendix B: WOMAC

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Appendix A: BPI-SF

STUDY ID #: _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

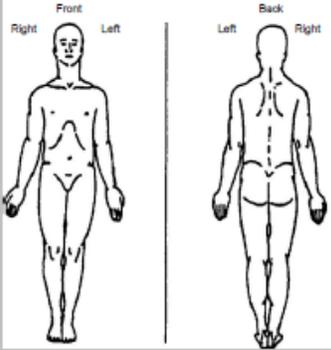
Date: ____/____/____ Time: _____

Name: _____
Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

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STUDY ID #: _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: ____/____/____ Time: _____

Name: _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No Complete
Relief Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity
0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

C. Walking Ability
0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

D. Normal Work (includes both work outside the home and housework)
0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

F. Sleep
0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

G. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not Completely
Interfere Interferes

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Appendix B

WOMAC OSTEOARTHRITIS INDEX VERSION LK3.1

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions are asked in the following format. Please mark your answers by putting an "X" in one of the boxes.

EXAMPLES:

1. If you put your "X" in the box on the far left as shown below,

none	mild	moderate	severe	extreme
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

then you are indicating that you feel no pain.

2. If you put your "X" in the box on the far right as shown below,

none	mild	moderate	severe	extreme
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

then you are indicating that you feel extreme pain.

3. Please note:

- that the further to the right you place your "X", the more pain you feel.
- that the further to the left you place your "X", the less pain you feel.
- please do not place your "X" outside any of the boxes.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 hours.

Think about your _____ (study joint) when answering the questions. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the arthritis in your _____ (study joint).

Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.

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PAIN

Think about the pain you felt in your _____ (study joint) caused by your arthritis during the last 48 hours.

(Please mark your answers with an "X".)

QUESTION: How much pain have you had . . .					Study Coordinator Use Only		
1. when walking on a flat surface?	none	mild	moderate	severe	extreme	PAIN1	_____
	<input type="checkbox"/>						
2. when going up or down stairs?	none	mild	moderate	severe	extreme	PAIN2	_____
	<input type="checkbox"/>						
3. at night while in bed? (that is - pain that disturbs your sleep)	none	mild	moderate	severe	extreme	PAIN3	_____
	<input type="checkbox"/>						
4. while sitting or lying down?	none	mild	moderate	severe	extreme	PAIN4	_____
	<input type="checkbox"/>						
5. while standing?	none	mild	moderate	severe	extreme	PAIN5	_____
	<input type="checkbox"/>						

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Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your _____ (study joint) caused by the arthritis during the last 48 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

(Please mark your answers with an "X".)

<p>6. How severe has your stiffness been after you first woke up in the morning?</p> <p>none mild moderate severe extreme</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>7. How severe has your stiffness been after sitting or lying down or while resting later in the day?</p> <p>none mild moderate severe extreme</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	<p>Study Coordinator Use Only</p> <p>STIFF6 _____</p> <p>STIFF7 _____</p>
--	---

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Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**. (Please mark your answers with an "X".)

QUESTION: How much difficulty have you had . . .					Study Coordinator Use Only	
8. when going down the stairs?	none	mild	moderate	severe	extreme	PFTN8 _____
	<input type="checkbox"/>					
9. when going up the stairs?	none	mild	moderate	severe	extreme	PFTN9 _____
	<input type="checkbox"/>					
10. when getting up from a sitting position?	none	mild	moderate	severe	extreme	PFTN10 _____
	<input type="checkbox"/>					
11. while standing?	none	mild	moderate	severe	extreme	PFTN11 _____
	<input type="checkbox"/>					
12. when bending to the floor?	none	mild	moderate	severe	extreme	PFTN12 _____
	<input type="checkbox"/>					
13. when walking on a flat surface?	none	mild	moderate	severe	extreme	PFTN13 _____
	<input type="checkbox"/>					

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DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**. (Please mark your answers with an "X".)

QUESTION: How much difficulty have you had . . .	Study Coordinator Use Only
14. getting in or out of a car, or getting on or off a bus? none mild moderate severe extreme <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	PFTN14 _____
15. while going shopping? none mild moderate severe extreme <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	PFTN15 _____
16. when putting on your socks or panty hose or stockings? none mild moderate severe extreme <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	PFTN16 _____
17. when getting out of bed? none mild moderate severe extreme <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	PFTN17 _____
18. when taking off your socks or panty hose or stockings? none mild moderate severe extreme <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	PFTN18 _____
19. while lying in bed? none mild moderate severe extreme <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	PFTN19 _____

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DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**. (Please mark your answers with an "X".)

QUESTION: How much difficulty have you had ...					Study Coordinator Use Only	
20. when getting in or out of the bathtub?	none	mild	moderate	severe	extreme	PFTN20 _____
	<input type="checkbox"/>					
21. while sitting?	none	mild	moderate	severe	extreme	PFTN21 _____
	<input type="checkbox"/>					
22. when getting on or off the toilet?	none	mild	moderate	severe	extreme	PFTN22 _____
	<input type="checkbox"/>					
23. while doing heavy household chores?	none	mild	moderate	severe	extreme	PFTN23 _____
	<input type="checkbox"/>					
24. while doing light household chores?	none	mild	moderate	severe	extreme	PFTN24 _____
	<input type="checkbox"/>					

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/s/

YASMIN A CHOUDHRY
01/17/2018

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01/17/2018

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