23 July 2020
EMA/423776/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

CRYSVITA

International non-proprietary name: burosumab

Procedure No. EMEA/H/C/004275/II/0010/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

1,25(OH)2D	1,25-dihydoxy vitamin D
6MWT	6-Minute Walk Test
ADRs	Adverse drug reactions
ACS	Aortic Calcium Scoring
AE	Adverse event
ALP	Alkaline phosphatase
AUC	Area under the plasma/serum concentration-time curve
BALP	Bone-specific alkaline phosphatase
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory- Short Form
BUN	Blood urea nitrogen
CCS	Coronary Calcium Scoring
CI	Confidence interval
CKD	Chronic kidney disease
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CTx	Carboxy-terminal cross-linked telopeptide of type I collagen
ECG	Electrocardiogram
ECHO	Echocardiogram
eGFR	Estimated glomerular filtration rate
EF	Ejection Fraction
EMA	European Medicines Agency
EOS	End of study
F	Bioavailability
FEP	Fractional excretion of phosphorus
FGF23	Fibroblast growth factor 23
GEE	Generalised estimating equation
GFR	Glomerular Filtration Rate
HR	Heart rate
HRQoL	Health-related quality of life
iPTH	Intact parathyroid hormone
ISR	Injection site reaction
KRN23	Burosumab
LLN	Lower limit of normal
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities

MCID	Minimal clinically important differences
MIC	Minimally important change
MLt	Mineralisation lag time
O.Th	Osteoid thickness
OS/BS	Osteoid surface/bone surface
OV/BV	Osteoid volume/bone volume
P1NP	Procollagen type 1 n-terminal propeptide
PD	Pharmacodynamic(S)
PGI-S	Patient Global Impression of Severity
PGI-I	Patient's Global Impression of Improvement
PHEX	Phosphate-regulating gene with homologies to endopeptidases on the X chromosome
PI	Phosphorous (inorganic)
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
QoL	Quality of life
QTc	Corrected QT interval
QTcB	QTc corrected for heart rate using Bazette’s formula
QTcF	QTc corrected for heart rate using Fridericia’s formula
RLS	Restless leg syndrome
RP	Role Limitations Due To Physical Health
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SE	Standard error
SF-36	36-Item Short Form Health Survey
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment-emergent adverse even
TmP/GFR	Ratio of renal tubular maximum reabsorption of phosphate to glomerular filtration rate
TRP	Tubular reabsorption of phosphate
TUG	Timed Up And Go
ULN	Upper limit of normal
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-linked hypophosphataemia

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Kyowa Kirin Holdings B.V. submitted to the European Medicines Agency on 27 August 2019 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include treatment of adults with X-linked hypophosphataemia (XLH), and modification of the currently approved indication in children and adolescents, by removing the qualification 'with growing skeletons', in order to include treatment in all children with radiographic evidence of bone disease.
The application provides new week-48 data from Study UX023-CL304; a randomized, double-blind, placebo-controlled, phase 3 study with open-label extension to assess the efficacy and safety of KRN23 in adults with XLH.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.1.
The updated RMP version 2.0 has also been submitted.

The group of variations requested amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

CRYSVITA was designated as an orphan medicinal product EU/3/14/1351 on 15 October 2014. Crysvita was designated as an orphan medicinal product in the following indication:

Treatment of X-linked hypophosphataemia

This was later amended by COMP in February 2018, following the assessment of an orphan designation maintenance report, to the following indication:

Treatment of hypophosphataemic rickets

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0007/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0007/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Jayne Crowe

Timetable	Actual dates
Submission date	27 August 2019
Start of procedure	2 November 2019
CHMP Rapporteur Assessment Report	20 December 2019
CHMP Co-Rapporteur Assessment Report	19 December 2019
PRAC Rapporteur Assessment Report	3 January 2020
PRAC members comments	9 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	22 January 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 January 2020
1st Request for supplementary information (RSI)	30 January 2020
CHMP Rapporteur response Assessment Report	28 May 2020
PRAC Rapporteur response Assessment Report	29 May 2020
PRAC Outcome	11 June 2020
CHMP members comments	17 June 2020
Updated CHMP Rapporteur response Assessment Report	18 June 2020
2nd Request for supplementary information (RSI)	25 June 2020

Timetable	Actual dates
CHMP Rapporteur response Assessment Report	8 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur Assessment Report	N/A
CHMP Opinion	23 July 2020

2. Scientific discussion

2.1. Introduction

X-linked hypophosphataemia (XLH) is characterised by high levels of circulating fibroblast growth factor 23 (FGF23) that leads to excessive urinary phosphate excretion and subsequent hypophosphataemia, resulting in defective bone mineralisation and impacts to other tissues such as muscle. The major pathologic consequences of XLH in bone are rickets, osteomalacia, fractures and bone deformities requiring surgical intervention. XLH in children is associated with substantial skeletal deformities that cause pain and impair physical functioning, such that a young child may be severely limited in his/her daily activities and will suffer lifelong disability, social stigmatisation, and pain as these deformities become a permanent structure of their bones. In adults, the chronic osteomalacia often leads to development of short stature, bowed limbs, pathologic fractures and pseudofractures, early osteoarthritis, and enthesopathies, which cause stiffness, and pain requiring use of analgesic drugs. These impairments may limit physical function and impact quality of life.

Conventional therapy for XLH consists of multiple daily doses of oral phosphate often combined with active vitamin D. Evidence of a positive effect of this therapy is limited and treatment can be cumbersome, and compliance is challenging. Furthermore, multiple daily doses of oral phosphate produce a transient and intermittent increase in serum phosphorus (Glorieux et al, 1980) that can exacerbate phosphate wasting because the impairment in renal phosphate reabsorption is not addressed. This intermittent phosphate load triggers high urinary phosphate excretion and increases risk and progression of nephrocalcinosis, which occurred in as many as 50%-100% of treated patients (Goodyer et al, 1987; Verge et al, 1991; Kooh et al, 1994; Carpenter et al, 2011; Sabbagh et al, 2008), and also in adolescents who would have received shorter periods of oral therapy (Zhukouskaya et al, 2019). Awareness of this safety risk led to the implementation of less aggressive, lower phosphate dosing strategies to reduce the risk of nephrocalcinosis in patients with XLH (Carpenter et al, 2011; Rafaelsen et al, 2016; Carpenter, 1997).

Burosumab is a recombinant fully human IgG1 monoclonal antibody that binds to and inhibits the excessive biological activity of FGF23, thereby treating the underlying cause of XLH. The European Commission granted a conditional marketing authorisation (MA) for Crysvita on 19 Feb 2018, for the treatment of XLH with radiographic evidence of bone disease in children ≥1 year of age and adolescents with growing skeletons (Authorisation No. EU/1/17/1262).
On 17 Apr 2018, burosumab was approved by the US FDA for the treatment of adults and children with XLH aged 1 year and older. Since approval in the EU and the US, burosumab has also been approved with the same indication in Canada (05 Dec 2018), the United Arab Emirates (12 Feb 2019) and Brazil (26 Mar 2019).

In the original MAA in the EU, the MAH pursued the adult indication, but subsequently elected to withdraw the application due to lack of sufficient data in adults at the time. The MAH now applies for an extension

of the currently approved indication to include also adults and adolescents who have attained peak vertical height or with closed growth plates.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The Applicant has submitted a justification for omitting an environmental risk assessment. According to the guideline on Environmental Risk Assessment of medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acid, peptides and proteins are exempted since they are unlikely to result in significant risk to the environment. Consequently, the justification provided is considered acceptable.

2.2.2. Conclusion on the non-clinical aspects

Considering the characteristics of the active substance, burosumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Table 1: Summary of Interventional Studies of Burosumab Contributing to the Assessment of Efficacy (Paediatric population)

Study Identifier and Title (Link to Study Report)	Phase	Population	Planned Length of Study and Burosumab Dose	Key Endpoints for Efficacy	Status
Paediatric Studies					
UX023-CL201 A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH) (UX023-CL201 Week 64 CSR), (UX023-CL201 Week 160 CSR)	2	XLH patients 5-12 years (N = 52)	160 weeks[a]; data available for all subjects to Week 160 Burosumab: Q2W 0.1-2.0 mg/kg Q4W 0.2-2.0 mg/kg	Primary Efficacy: Change from baseline in severity of rickets as measured by RSS total score PD: Serum phosphorus, serum $1,25(OH)_2D$, TmP/GFR	Completed
UX023-CL205 An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics, and Efficacy of KRN23 in Children from 1 to 4 Years Old with X-linked Hypophosphatemia (XLH) (UX023-CL205 Week 40 CSR)	2	XLH patients 1-4 years (N = 13)	64 weeks[a]; data available for all subjects to Week 40 Burosumab: Q2W 0.8 or 1.2 mg/kg	Primary Efficacy: Change from baseline over time in serum phosphorus PD: Change from baseline over time in serum $1,25(OH)_2D$ and urinary phosphorus	Ongoing
UX023-CL301 A Randomized, Open-Label, Phase 3 Study to Assess the Efficacy and Safety of KRN23 Versus Oral Phosphate and Active Vitamin D Treatment in Pediatric Patients with X-linked Hypophosphatemia (XLH) (UX023-CL301 Week 64 CSR)	3	XLH patients 1-≤12 years (N = 61)	140 weeks; data available for Week 64 for all subjects. Burosumab: 0.8 mg/kg Q2W (up to 1.2 mg/kg Q2W)	Primary efficacy: change in rickets at Week 40 as assessed by the RGI-C global score.	Ongoing

Table 2: Summary of Interventional Studies of Burosumab Contributing to the Assessment of Efficacy (Adult population)

Study Identifier and Title (Link to Study Report)	Phase	Population	Planned Length of Study and Burosumab Dose	Key Endpoints for Efficacy	Status
Adult Studies					
KRN23-INT-001 A Phase 1/2, Open-Label, Repeat-Dose, Dose-Escalation Study of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (KRN23-INT-001 Final CSR)	1/2	XLH patients ≥18 years (N = 32; 28 burosumab, 1 placebo; 3 subjects discontinued before treatment)	120 days Burosumab SC Q4W 0.05, 0.1, 0.3 and 0.6 mg/kg	Primary Efficacy: Number and % subjects with postdose serum phosphorus levels ≤2.5, >2.5 but ≤ 3.5, >3.5 but ≤4.5 mg/dL, and >4.5 mg/dL PD: Change from baseline in serum phosphorus and other serum PD measures, urinary PD measures, sex hormones, bone biomarkers	Completed
KRN23-INT-002 An Open-Label, Long-Term, Extension Study to Evaluate the Safety and Efficacy of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (KRN23-INT-002 Final CSR)	1/2	XLH patients ≥18 years (N = 23; 22 burosumab, 1 placebo)	12 months burosumab SC Q4W 0.1, 0.3, 0.6, and 1.0 mg/kg	Primary Efficacy: Number and % subjects with postdose serum phosphorus levels ≤2.5, >2.5 but ≤3.5, >3.5 but ≤4.5 mg/dL, and >4.5 mg/dL PD: Change from baseline in serum phosphorus and other serum PD measures, urinary PD measures, sex hormones, bone biomarkers	Completed

Study Identifier and Title (Link to Study Report)	Phase	Population	Planned Length of Study and Burosumab Dose	Key Endpoints for Efficacy	Status
UX023-CL203 A Phase 2b, Open-Label, Long-Term Extension Study to Evaluate the Safety and Pharmacodynamics of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (XLH) (UX023-CL203 Week 48 CSR)	2b	XLH patients ≥18 years (N = 20)	194 weeks; data available for all subjects to Week 48 (data cut-off of 08 Jun 2017) Burosumab SC Q4W 0.3, 0.6, and 1.0 mg/kg	PD: Number and % subjects with postdose serum phosphorus levels in the normal range; other serum PD measures, urinalysis parameters, bone biomarkers Exploratory Efficacy: Changes in pain, stiffness, HRQoL (by BPI, WOMAC, SF-36), 6MWT, TUG test	Ongoing
UX023-CL303 A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study with Open-Label Extension to Assess the Efficacy and Safety of KRN23 in Adults with X-linked Hypophosphatemia (XLH) (UX023-CL303 Week 24 CSR), (UX023-CL303 Week 48 CSR)	3	XLH patients 18-65 years (N = 134; 68 burosumab, 66 placebo)	96 weeks[a]; data available for all subjects to Week 48 (data cut-off of 08 Jun 2017) Burosumab SC Q4W 1.0 mg/kg or Placebo SC Q4W	Primary Efficacy: % of subjects achieving mean serum phosphorus levels above the LLN across the midpoints of the dose intervals between baseline and Week 24 Key Secondary Efficacy: Changes from baseline to Week 24 in BPI Worst Pain and WOMAC Stiffness and Physical Function	Ongoing

Study Identifier and Title (Link to Study Report)	Phase	Population	Planned Length of Study and Burosumab Dose	Key Endpoints for Efficacy	Status
UX023-CL304 An Open-Label, Single-Arm, Phase 3 Study to Evaluate the Effects of KRN23 on Osteomalacia in Adults with X-linked Hypophosphatemia (XLH) (UX023-CL304 Interim Report), (UX023-CL304 Week 48 CSR)	3	XLH patients 18-65 years (N = 14)	96 weeks[a]; baseline and Week 48 bone biopsy data available for 11 evaluable subjects (data cut-off of 30 Aug 2017) Burosumab SC Q4W 1.0 mg/kg	Primary Efficacy: Percent change from baseline in osteoid volume/bone volume (OV/BV) at Week 48 based on analysis of iliac crest bone biopsies Key Secondary Efficacy: Serum phosphorus levels	Ongoing

a: Planned study duration as of data snapshots for the study data included in this summary. After the study snapshots, the planned study duration was increased for UX023-CL205 to up to 160 weeks, for UX023-CL303 to up to 157 weeks, and for UX023-CL304 to up to 144 weeks.
BPI = Brief Pain Inventory; CSR = Clinical Study Report; FGF23 = fibroblast growth factor 23; GFR = glomerular filtration rate; HRQoL = health-related quality of life; LLN = lower limit of normal; 1,25(OH)2D = 1,25dihydroxyvitamin D; 6MWT = 6 minute walk test; OV/BV = osteoid volume/bone volume; PD = pharmacodynamics; Q2W = once every 2 weeks; Q4W = once every 4 weeks; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score SC = subcutaneous; SF-36 = 36-item short form survey; TmP = renal tubular maximum reabsorption rate of phosphate; TUG = Timed Up and Go; WOMAC = Western Ontario and McMaster Universities Arthritis Index; XLH = X-linked hypophosphataemia.

2.3.2. Pharmacokinetics

To support the current variation, the focus will be on the burosumab PK and PD data in adult XLH patients. Data are available from seven adult clinical trials, KRN23-US-02, KRN23-001, KRN23-INT-001, KRN23-INT-002, UX023-CL203, UX023-CL303 and UX023-CL304. To support the characterisation of burosumab PK and PK/PD, modelling and simulations were performed using data from the aforementioned adult studies, and PK and PD data from paediatric XLH patients, who were enrolled in three clinical trials UX023-CL201, UX023-CL205, and UX023-CL301. Further, modelling using data from these studies were used to support dosing in adolescent patients who have XLH.

In summary, following single or repeat dose SC administrations, burosumab serum concentrations displayed an approximate mono-exponential decline. Apparent elimination half-life (t1/2) values, e.g., 394 hours approximately 16 days, after repeat SC administrations in Study KRN23-INT-001). Dose-linear, time-invariant PK were observed within a repeat SC dose range of 0.05-1.0 mg/kg. The absolute bioavailability from SC administration was determined to be approximately 100%.

Analytical methods

No new data regarding the comparability of formulations and the pharmacokinetic (PK) and neutralizing antibody (Nab) assays have been generated, which is acceptable. Assays to measure burosumab concentrations in serum (PK), and to evaluate immunogenicity (anti-drug antibodies [ADA]) and total and free (unbound) FGF23, serum phosphorus and bone turnover markers were described in the initial MAA. The updated assay methodology employed to detect ADA using an assay method with an increased drug tolerance limit is described below.

Immunogenicity

The method development approach taken for the new assay for ADA was dependent on the concept of separating the burosumab-ADA antibody complex and then assaying the resulting free ADA. This separation was accomplished in multiple steps: acidification and neutralization of the serum sample to free ADA from burosumab, immobilization of ADA by burosumab bound to solid phase bead, followed by

washing and extraction of ADA from the bead by acid dissociation, and final neutralization in storage buffer.

Population Pharmacokinetic Analysis

A unified population PK model was first developed for all study subjects from the 2 paediatric studies, and 5 adult studies. Second updated analyses were conducted, which included additional longitudinal data from UX023-CL303 and subjects from adult study UX023-CL304 and paediatric study UX023-CL301. These studies included 94 children ≤12 years of age (6 subjects <2 years, 88 subjects 2-12 years of age) and 183 unique adult subjects. In total, the dataset for the population analysis included 2844 measurable serum concentrations of burosumab (PK) and 6047 measurable concentrations of serum phosphorus (PD) collected in 277 unique XLH trial subjects. The dose range studied ranged from 0.05 to 2.0 mg/kg by SC administration, and two dosing frequencies (Q2W and Q4W) were included. The clinical trials included in the PK and PK/PD modelling analyses are summarised in Table 5.

Table 3 Summary of KRN23 PK Data Used for Population PK and PK/PD Modelling in Adult and Paediatric Subjects with XLH

Protocol Number	Study Title	Dosing Route & Dose Regimens	Subjects and Number	Planned PK/PD Sampling
KRN23-US-02	A Phase I, double-blind, randomized, placebo-controlled, single-dose, dose-escalation study of KRN23 in XLH Patients	Single SC doses (0.1, 0.3, 0.6 and 1.0 mg/kg)*	12 adult subjects	For all SC treatment on Day -1 (1 day prior to dose); and days 1 to 50 at 4, 8, 12, 24, 48, 60, 72, 84, 96, 168, 336, 504, 672, 840, 1008, 1176 h post dose. Two additional samples for 0.6 and 1.0 mg/kg SC at 264 (Day 12) and 408 (Day 18) h post-dose
KRN23-INT-001	A Phase I/II, open-label, repeat-dose, dose-escalation study of KRN23 in adult subjects with XLH	Starting SC dose of 0.05 mg/kg followed by escalating SC doses 0.10, 0.30 and 0.60 mg/kg Q4W (up to 4 doses), dose adjustment was based on serum phosphorus level and safety evaluations.***	29 adult subjects	Pre-dose and post-dose at Days 0, 3, 7, 12, 18, 26, 28, 31, 35, 40, 46, 54, 56, 59, 63, 68, 74, 82, 84, 87, 91, 96, 102, 110 and at the end of study (Day 120) or early withdrawal (~6-7 samples/dose)
KRN23-INT-002	An open-label, long-term, extension study to evaluate the safety and efficacy of KRN23 in adult subjects with XLH.**	Subjects received SC dose of 0.05, 0.10, 0.30, 0.60 and 1.0 mg/kg Q4W (up to 12 doses), dose adjustment based on serum phosphorus level and safety evaluations.***	22 adult subjects who participated in KRN23-INT-001 study	Pre-dose for each Dose Visit; Post dose at Visits 46, 47, 48, 49, 50 (follow up visit) and at early withdrawal
UX023-CL203	APphase 2b, open-label, long-term extension study to evaluate the safety and pharmacodynamics of KRN23 in adult subjects XLH	SC dose of burosumab Q4W, from Week 0 through Week 140 of the study. The starting dose of burosumab at Baseline (Week 0) (0.30, 0.60, or 1.0 mg/kg).	19 subjects who participated in Study KRN23-INT-001 or KRN23-INT-002	PK: Week 24, 36, 48, 72 PD:D-1, Weeks 0, 2, 4, 6, 8, 10, 12, 24, 26, 28, 36, 38, 40,48, 50, 52, 60, 72,
UX023-CL303	A randomized, double-blind, placebo-	Randomised ~1:1 to receive burosumab 1 mg/kg (rounded	134 adult subjects	PK: Weeks 1, 2, 4, 21, 22, 24, 34, 36,

Protocol Number	Study Title	Dosing Route & Dose Regimens	Subjects and Number	Planned PK/PD Sampling
	controlled, phase 3 study with Open-label extension to assess the efficacy and safety of KRN23 in adults with XLH	to the nearest 10 mg) or placebo administered SC Q4W for 24 weeks (subjects in placebo arm crossed over to burosumab treatment after Week 24)	(68 randomised to burosumab treatment)	46 and 48 PD: Week -4, Predose, Week 0, 1,2, 4, 6, 10, 12, 14, 18, 20, 21, 22, 24, 26, 28, 34, 36, 46 and 48
UX023-CL304	An open-label, single arm, phase 3 study to evaluate the effects of KRN23 on osteomalacia in adults with XLH	1.0 mg/kg KRN23 (rounded to the nearest 10 mg) administered SC monthly weeks (Q4W, 28 days) for 48 weeks. Subjects who complete the 48 weeks of the open-label treatment period will then continue into an additional 48-week treatment extension period I (until Week 96).	14 patients	PK: peak and trough samples were collected at Week 1, 2,4, 21, 22, 24, 48, 64 and 68 PD: Week -4, Week 1,2, 4, 6, 12, 14, 20, 21, 22, 24, 28, 36, 48, 60, 70, 72 and 84
UX023-CL201	A randomized, open-label, dose finding, Phase 2 study to assess the pharmacodynamics and safety of the anti-FGF23 antibody, KRN23, in pediatric (5-12 years) patients with XLH	SC dosing Q2W or Q4W, during titration and treatment period: Q2W for all subjects during the extension period for a total of 160 weeks. Dose adjusted based on phosphorus levels, if required.	52 paediatric subjects aged 5-12 inclusive	PK: Predose at Baseline, Weeks 1, 2, 4, 12, 14, 16, 36, 38 and 40 PD: Predose at Screening, Baseline, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 28, 30, 32, 36, 38, 40 and 46

Protocol Number	Study Title	Dosing Route & Dose Regimens	Subjects and Number	Planned PK/PD Sampling
UX023-CL205	A randomized, open-label, dose finding, phase 2 study to assess the pharmacodynamics and safety of the anti-FGF23 antibody, KRN23, in pediatric (1-4 years) patients with XLH	Starting dose of 0.8 mg/kg Q2W SC for a total of 64 weeks. The dose may have been increased to 1.2 mg/kg at any time during the study if a subject meets the following dose-adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus.	13 paediatric subjects aged 1-4 inclusive	PK: Predose at Weeks 1, 2, 4, 12 and 40 PD: Predose at Screening, Weeks 1, 4, 8, 12, 15, 20, 26, 32, 40, 48, 56, 64 and 76
UX023-CL301	A randomized, open-label, Phase 3 study to assess the efficacy and safety of KRN23 versus oral phosphate and active vitamin D treatment in pediatric patients with XLH	0.8 mg/kg Q2W SC or oral phosphate and active vitamin D therapy for a total of 64 weeks in the treatment period. After completion of the 64-week Treatment Period, subjects in Europe, the US, Canada, and Australia who were randomised to burosumab continued treatment with burosumab at their previous regimen and those randomised to active control were to cross over to receive burosumab 0.8 mg/kg Q2W SC.	29 paediatric subjects aged 1-12 inclusive	PK: Week 1, 2, 4, 8, 16, 24, 33, 40 and 64 PD: Screening, Week 0, 1, 2, 4, 8, 12, 16, 24, 32, 33, 40, 52 and 64

PD = pharmacodynamic; PK = pharmacokinetic; Q2W = once every 2 weeks; Q4W = monthly, once every four weeks; SC = subcutaneous; US = United States; XLH= X-linked hypophosphatemia.

* Intravenous treatments and placebo group were not considered in the analysis.

** Subjects who satisfactorily completed KRN23-INT-001 study were eligible to be treated in KRN23-INT-002 study.

***A placebo group was included in the bone sub study but was excluded from analysis.

Non-Linear Mixed Effect (NLME) population PK and PK/PD analyses were performed using Phoenix NLME v8 (Pharsight – A Certara Company). Dataset exploration, figures and tables, as well as posterior Bayes estimation of parameter values for individual subjects were performed using R V3.5 with comprehensive R archive network (CRAN) and Certara Strategic Consulting (CSC) package.

The PK of burosumab were described using a model with SC absorption with first-order kinetics, one-compartment distribution post absorption, and concentration-independent and time-invariant clearance from circulation. Hypothesis of non-linear clearance of burosumab in the form of Michaelis-Menten kinetics was specifically tested and rejected due to deterioration in model fitting.

In the original combined paediatric and adult model using 7 studies, the body weight (WT) based allometric scaling of CL/F and V/F was incorporated in the model, and the data estimated allometric scalars were 0.89 and 1.0, respectively, supporting body weight normalised dosing of burosumab. Evaluated covariates included sex, ethnicity/race, country of clinical trials (including the US and Japan), status of anti-burosumab antibody, time-varying intact FGF23, baseline ALB, baseline ALP, baseline ALT,

baseline creatinine and baseline CRCL. Baseline levels of creatinine clearance (CRCL) were derived based on Schwartz equation for paediatric population and based on Cockcroft and Gault equation for adult population. Search for significant covariates also included types of PHEX mutation of subjects, which are categorised into 3 classes: (1) pathogenic mutations and likely pathogenic mutations; (2) variants of uncertain significance; and (3) likely benign and no mutation. After including the WT effects on CL/F and V/F, no other covariates were found to be significant predictor of burosumab disposition. A step-wise covariate model building procedure was used. Table 11 summarises estimated burosumab population PK parameters in XLH patients.

The updated model included additional data from UX023-CL303, and subject data from adult study UX023-CL304 and paediatric study UX023-CL301. A summary of the data included in the updated model development (i.e. all PK data used in the population PK analysis) is presented in Table 6, Table 7, Table 8, and Table 9. Serum concentrations of burosumab reported as BLQ (i.e., <36 and <50 ng/mL, depending of the study) were flagged and set to missing for the population PK analysis of XLH population.

Table 4 Summary of Continuous Demographic Data at Baseline in Patients with XLH

Continuous Covariates	Mean (CV%) Median [Minimum-Maximum]		
	Infants (1 month - 2 years old) N=6	**Children (2 – 12 years old) N=88**	**Adults (>17 years old) N=183**
Age (years)	1.30 (28.8%) 1.30 [0.800*, 1.80]	7.28 (38.7%) 8.00 [2.20, 12.8]	40.6 (30.3%) 41.0 [18.5, 68.0]
Body mass index (kg/m^2)	17.2 (9.28%) 16.9 [15.4, 20.1]	20.2 (32.4%)[a] 18.6 [14.2, 67.8]	31.0 (26.6%)[b] 30.1 [17.4, 68.2]
Height (cm)	78.3 (5.63%) 78.2 [72.5, 85.3]	111 (15.8%)[a] 111 [54.6, 146]	152 (6.99%)[b] 150 [121, 176]
Weight (kg)	10.5 (13.0%) 10.4 [9.00, 12.7]	25.7 (41.4%) 23.4 [9.20, 55.2]	71.5 (26.8%) 69.0 [36.1, 140]

CV= Coefficient of variation; N= Number of patients; XLH= X-linked hypophosphatemia.
* Age at screen; the subject was 1 year old when she received the 1st burosumab dose.
[a]: N = 86; [b]: N = 181.
Note 1: Height and body mass index were missed for 2 patients in Study UX023-CL201 (patient UX023-CL201-138-022 and patient UX023-CL201-148-001) and one patient (UX023-CL303-142-302) in Study UX023-CL303. Height and body mass index of patient UX023-CL303-142-309 in Study UX023-CL303 were considered as outlier and were excluded from the summary statistics.
Note 2: Number of adult subjects was based on the unique subject identifier (USUBJID); 26 patients were enrolled in more than one trial.

Table 5 Summary of Categorical Demographic Data at Baseline in Patients with XLH

Covariate	N (%)		
	Infants (1 month - 2 years old) N=6	**Children (2 – 12 years old) N=88**	**Adults (>17 years old) N=183**
Sex			
Male	4 (67 %)	42 (48 %)	67 (37 %)
Female	2 (33 %)	46 (52 %)	116 (63 %)
Race			
White	5 (83 %)	78 (89 %)	151 (83 %)
Black or African American	0 (0 %)	3 (3 %)	5 (3 %)
Asian	1 (17 %)	1 (1 %)	25 (14 %)
Other	0 (0 %)	6 (7 %)	2 (1 %)
Class of PHEX mutation			
LPATH	1 (17 %)	7 (8 %)	119 (65 %)
PATH	4 (67 %)	75 (85 %)	21 (11 %)
VUS	1 (17 %)	4 (5 %)	18 (10 %)
Negative	0 (0%)	0 (0%)	10 (5 %)
Missing	0 (0%)	2 (2.3%)	15 (8 %)
Anti-Burosumab Antibody*			
Negative	5 (83%)	76 (86%)	172 (94 %)
Positive	1 (17%)	12 (14%)	11 (6 %)

ADA = Anti-burosumab antibody; LPATH = Likely pathological mutation; N = Number of patients; PATH = Pathological mutation; PHEX = Phosphate-regulating gene with homology to endopeptidase located on the X chromosome; VUS = Variants of uncertain significance; XLH= X-linked hypophosphatemia.

* Presence of anti-burosumab antibody if at least one time sample was positive.

Note: Number of adult subjects was based on the unique subject identifier (USUBJID); 26 subjects were enrolled in more than one trial.

Table 6 Summary of Serum Chemistry Test Results at Baseline in Subjects with XLH

Serum Chemistry Test	Mean (CV%) Median [Minimum-Maximum]		
	Infants (1 month - 2 years old) N=6	Children (2 – 12 years old) N=88	Adults (>17 years old) N=183
Bone alkaline phosphatase (µg/L)	172 (59.6%)[a] 127 [99.4, 289]	161 (37.9%)[b] 155 [13.0, 396]	25.0 (67.8%)[c] 19.0 [3.00, 91.0]
Serum albumin (g/dL)	4.60 (3.64%) 4.60 [4.40, 4.90]	4.46 (5.55%) 4.50 [3.80, 5.30]	4.33 (6.87%) 4.30 [3.40, 5.30]
Serum alkaline phosphatase (U/L)	564 (33.8%) 538 [286, 817]	482 (25.7%) 470 [237, 980]	122 (41.5%) 113 [26.0, 338]
Serum alanine aminotransferase (U/L)	18.0 (33.7%) 15.5 [13.0, 27.0]	15.9 (31.3%) 15.0 [5.00, 31.0]	25.1 (66.3%) 20.0 [7.00, 98.0]
Estimated creatinine clearance (mL/min/1.73m^2) in pediatric subjects (mL/min) in adult subjects	230 (52.5%) 191 [146, 469]	169 (21.4%)[d] 167 [100, 255][d]	146 (39.9%) 131 [49.9, 387]
Serum total intact fibroblast growth factor 23 (pg/mL)	300 (33.1%)[e] 341 [191, 400]	326 (125%) 161 [33.0, 2390]	142 (185%)[f] 76.1 [15.0, 2270]

CV= Coefficient of variation; N= Number of subjects; XLH= X-linked hypophosphatemia.
[a]: N = 3; [b]: N = 62, [c]: N = 180, [d]: N = 86, [e]: N = 5,[f]: N = 166
Note: Number of adult subjects was based on the unique subject identifier (USUBJID); 26 subjects were enrolled in more than one trial.

Table 7 Number of Serum PK Samples Available for the Population PK Modelling

PK Samples	N (% within age group)			
	Infants (1 month - 2 years old) (n=37)	Children (2 – 12 years old) (n=912)	Adults (>17 years old) (n=2230)	Overall (n=3177)
BLQ	0 (0%)	52 (5.8%)	281 (12.6%)	333 (10.5%)
Include	37 (100%)	860 (94.2%)	1947 (87.3%)	2844 (89.5%)

ALQ= Above the limit of quantification (>9500 µg/mL); BLQ= Below the limit of quantification (Study specific: <36.0 or 50.0); N= Number of samples; PK= Pharmacokinetic
Note: All BLQ and ALQ concentrations were excluded from the population PK analysis. One sample in Study KRN23-US-02 was excluded due to potential switch with intravenous administration
BLQ observed in blood samples from subjects enrolled in the placebo group were not included in the calculation
Note: In adult study UX023-CL203, two samples were ALQ of this specific study (i.e., >9500 ng/mL).

The inclusion of the additional data resulted in minor changes to the primary parameter estimates. The exponents in the allometric power function of effect of WT on CL/F and V/F (i.e., $[WT/70]^{effect}$) were estimated to be 0.877 and 0.972, respectively, and the 95% CI of the exponent of V/F included 1. The other change to the model structure was the simplification of the model through the elimination of the IOV effect due to high shrinkage and the incorporation of an additive plus proportional residual error model. In the modelling exercise, no new covariates were identified. Further, age or age population was not a significant covariate to influence burosumab PK, after the effect of WT had been included in the structural PK model. Table 11 summarises estimated burosumab population PK parameters in XLH patients using the updated model. Given the similarities in the results of the modelling exercises,

simulations supporting adolescent dosing and exposure-response investigation provided below were conducted using the original PK model. The estimated elimination t1/2 is slightly dependent on body weight and ranges from ~ 16 days for a typical young paediatric subject of 1-4 years old to ~ 19 days for a typical adult subject.

Table 8 Summary of Estimated Burosumab Population Typical PK Parameters in XLH Patients – Original Model

Parameters		Typical Values (RSE%)	BSV	IOV
PK Parameters	Ka (day^{-1})	0.380 (7.18)	0 (fixed)	
	V/F (L)	8.03 (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 (fixed)		
Error Model	Proportional Error (%)	20.2 (3.60)		

Parameter values are based on body weight of 70 kg. BSV= between-subject variability; IOV=inter-occasion variability; CL/F = apparent clearance; Ka = first-order rate of absorption; PK= pharmacokinetic; RSE = relative standard error; V/F= apparent central volume of distribution; WT= body weight (kg); XLH = X-linked hypophosphatemia.
Shrinkage: CL/F: 22.0%;V/F: 39.5%.
Source: Report ULTR-CSC-105, Table 8.

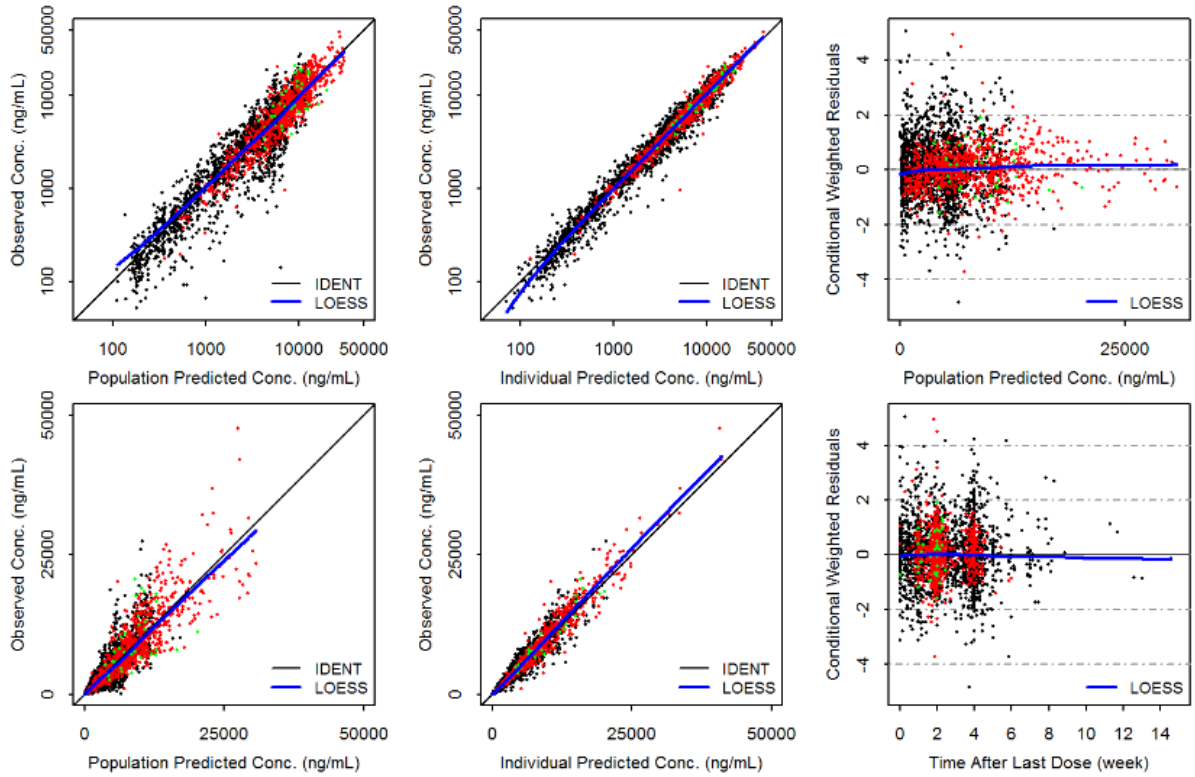
Table 9 Summary of Estimated Burosumab Population Typical PK Parameters in XLH Patients – Updated Model

Parameters		Typical Values (RSE)	BSV (Shrinkage)
PK Parameters	Ka (1/day)	0.389 (8.42%)	0 (Fixed)
	V/F (L)	7.57 (3.11%)	32.4% (20.9%)
	CL/F (L/day)	0.284 (2.60%)	31.8% (5.29%)
Covariate on CL/F	(WT/70)effect	0.877 (3.53%)	
Covariate on V/F	(WT/70)effect	0.972 (3.35%)	
Residual errors	Additive error (ng/mL)	30.3 (17.7%)	
	Proportional error (%)	19.6 (26.0%)	

BSV = between-subject variability; CL/F = apparent clearance; Ka = first-order rate of absorption; PK = pharmacokinetic; RSE = relative standard error; V/F = apparent central volume of distribution; WT = body weight (kg), XLH = X-linked hypophosphatemia.
Note: Effect of baseline WT was centralised using 70 kg to facilitate the integration of adult data.
Source: Report ULTR-CSC-106, Table 8.

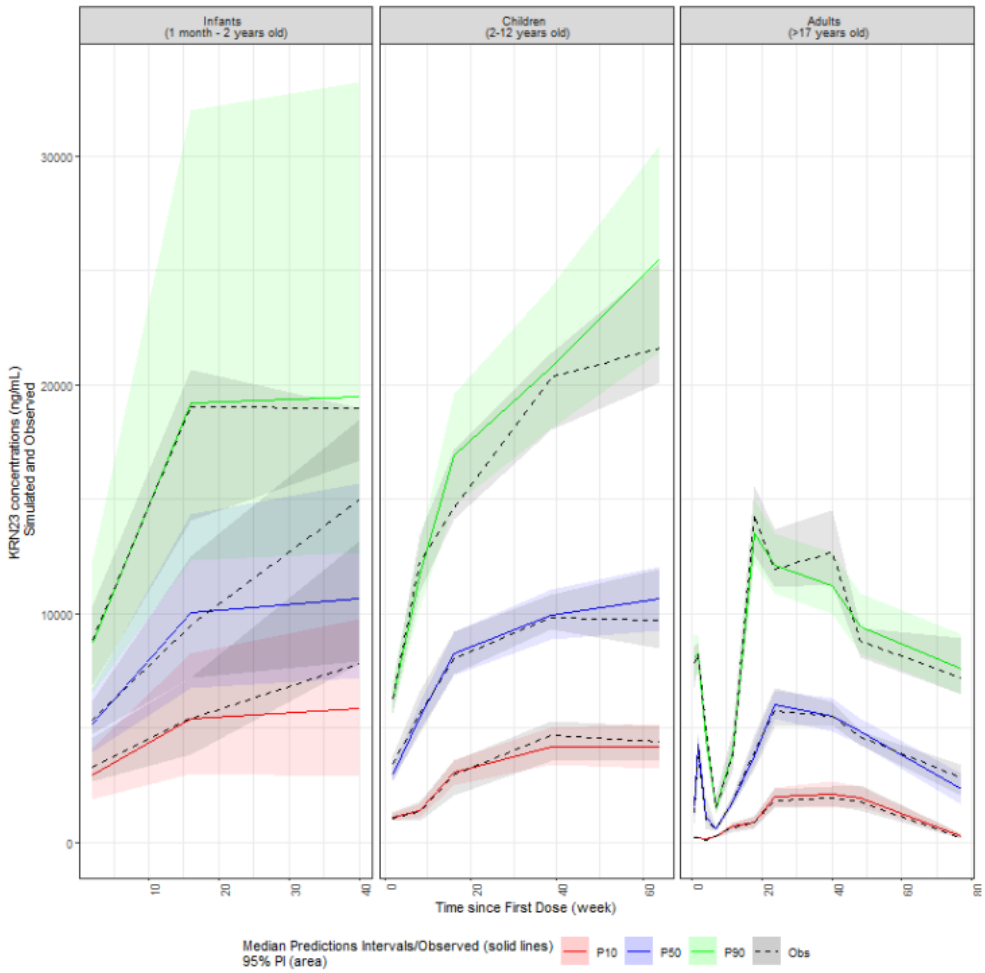
The PK model was evaluated through goodness-of-fit diagnostics and visual predictive checks, as displayed in Figure 2and Figure 3, respectively.

Figure 1 Goodness-of-Fit Updated Population PK Model of Burosumab in Patients with XLH



Green circles= infants with XLH; Red circles = children with XLH, Black circles = adults with XLH.
Conc = Concentration; IDENT= Line of identity; LOESS = Locally weighted scatter plot smoothing; PK = Pharmacokinetic; XLH= X-linked hypophosphatemia
Note 1: Observed concentrations vs. individual and population predicted concentrations are presented on log scales in the upper left and upper central plots, and in linear scales in the lower left and lower central plots.
Note 2: Age categories are infants (1 month-2 years old), children (2- 12 years old) and adults (>17 years old)

Figure 2 Visual Predictive Check for Subcutaneous Administration of Burosumab in Patients with XLH



Obs= Observations; P10= 10th percentile; P50= 50th percentile; P90= 90th percentiles; PI= Prediction interval; PK= Pharmacokinetic; XLH= X-linked hypophosphatemia.
Note: dashed lines represent percentiles of observed burosumab concentrations within each bin (95th percentiles in green, 50th percentiles in blue and 5th percentiles in red); shaded area represent 95% percentile interval of percentiles of predicted concentrations (95th percentiles in green, 50th percentiles in blue and 5th percentiles in red).

Population PK analysis **(Report ULTR-PMX-1280)**

A total of 277 patients (6 infants, 88 children and 183 adults) with XLH treated with burosumab were included in the population PK analysis. Descriptive statistics of demographic data and serum chemistry of included subjects are described. The current analysis adds longer follow-up PK and PD data from subjects in Studies UX203-CL201 and UX203-CL303, and updated immunogenicity data in Studies UX023-CL205, UX023-CL201 and UX203-CL303 for antidrug (burosumab) antibodies (ADA) based on an improved assay method.

The total number of serum concentrations available for the development of the population PK model of burosumab is presented in the table below. All BLQ and ALQ samples were excluded from the analysis.

Table 6 Number of Serum PK Samples Available for the Population PK Modeling

PK Samples	N (% within age group)			
	Infants 1 - 2 years old at the 1st dose treatment (N=37)	Children (2 - 12 years old) (N=1111)	Adults (>17 years old) (N=3292)	Overall (n=4440)
AQL	0 (0 %)	0 (0 %)	2 (0 %)	2 (0 %)
BLQ	0 (0 %)	52 (5 %)	858 (26 %)	910 (20 %)
Exclude	0 (0 %)	0 (0 %)	1 (0 %)	1 (0 %)
Include	37 (100 %)	1059 (95 %)	2431 (74 %)	3527 (79 %)

ALQ= Above the limit of quantification (>9500 µg/mL); BLQ= Below the limit of quantification (Study specific: <36.0 or 50.0); N= Number of samples; PK= Pharmacokinetic
Note: All BLQ and ALQ concentrations were excluded from the population PK analysis. One sample in Study KRN23-US-02 was excluded due to potential switch with intravenous administration
BLQ observed in blood samples from subjects enrolled in the placebo group were not included in the calculation
Note: In adult study UX023-CL203, two samples were ALQ of this specific study (i.e., >9500 ng/mL).

Amongst patients with immunogenicity information (not available in Study KRN23-US-02), a total of 48 unique subjects had at least one sample with confirmed presence of ADA. Among these 48 subjects, due to the conservative cut-off of ADA assays, 33 subjects had positive ADA in serum samples collected before the 1st burosumab dose. Only 3 patients in Study UX023-CL201, had samples with positive NAb. Most of the patients had only one or two samples with confirmed presence of ADA followed by seroreversion (i.e., from ADA positive to negative). Only a few patients had more than two samples with confirmed presence of ADA.

A previously developed one-compartment model with body weight (WT) based allometric functions on CL/F and V/F along with a first-order rate of absorption from SC injection sites was used as the starting point.

Impact of ADA and NAb status on PK parameters of burosumab were formally evaluated with the following three approaches:

- Time-invariant approach: Subjects were flagged as positive if at least one of their ADA sample had detectable ADA; other subjects were flagged as negative.
- Time-varying approach: PK samples and dose events were flagged as positive if ADA sample collected during the same day had detectable ADA or NAb, and were flagged as negative if no detectable ADA or NAb. Last-observation carried forward was applied for days without ADA sample.
- Time-latent approach: Introduce a latent variable ρ which is a continuous variable set to 0 for all negative ADA and NAb samples, and set to 1 for positive samples. At time points between measurements, a sigmoid function with estimated onset and offset times was used to interpolate ρ as a function of time.

For each of the three analysis methods, the presence of ADA did not have statistically significant influence on burosumab clearance. Due to the small number (N=3) of subjects who tested positive for NAb, a statistically meaningful analysis of NAb as an independent potential PK covariate is not possible.

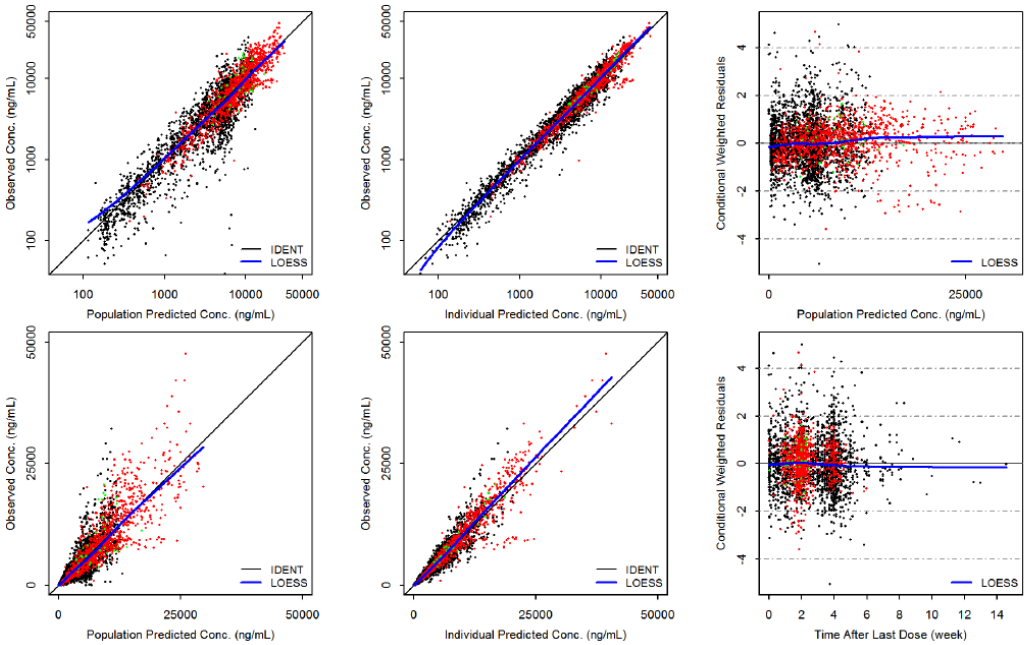
The population mean parameter estimates (based on a representative XLH subject of 70 kg) and their associated uncertainties are presented in Table 9. The diagnostic plots and VPC plots are provided in Figure 6 and Figure 7, respectively.

Table 9 Typical Values of the Final Population PK Model of Burosumab in Patients with XLH

	Parameters	Typical Values (RSE)	BSV (Shrinkage)
PK Parameters	Ka (1/day)	0.386 (8.3%)	0 fix
	V/F (L)	7.35 (3.0%)	31.7% (18.2%)
	CL/F (L/day)	0.278 (2.5%)	32.9% (3.9%)
Covariate on CL/F	$(WT/70)^{effect}$	0.876 (3.8%)	
Covariate on V/F	$(WT/70)^{effect}$	0.913 (3.6%)	
Residual errors	Additive error (ng/mL)	29.0 (17.6%)	
	Proportional error (%)	22.0 (18.4%)	

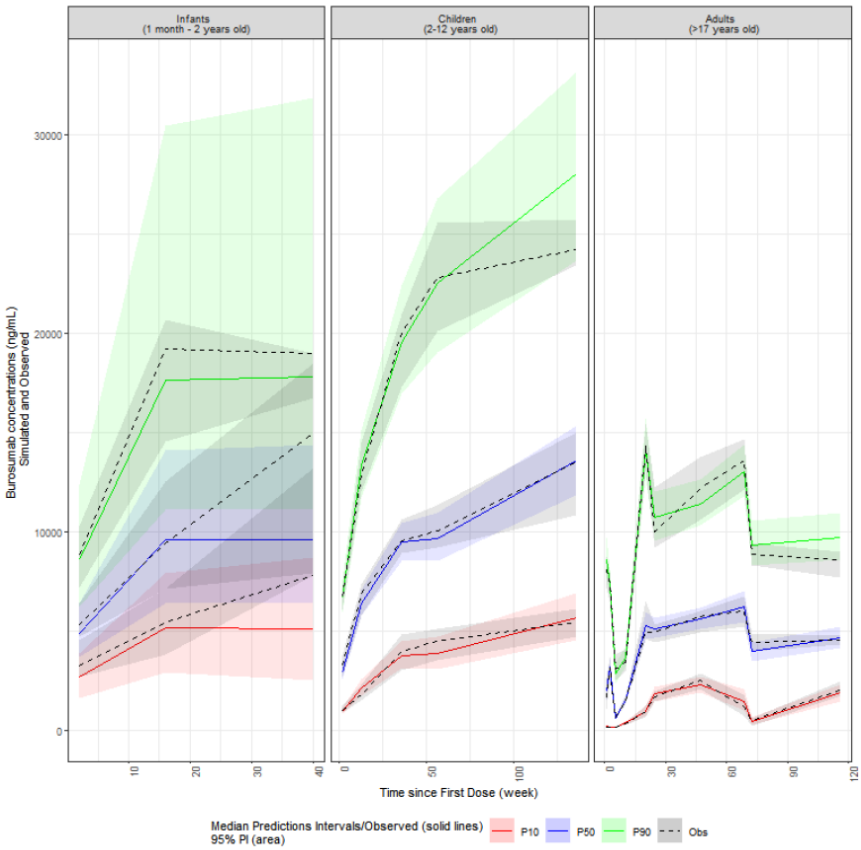
BSV= Between-subject variability; CL/F= Apparent clearance; Ka= First-order rate of absorption; PK= Pharmacokinetic; RSE = Relative standard error; V/F= Apparent central volume of distribution; WT= Body weight (kg), XLH= X-linked hypophosphatemia.
Note: Effect of baseline WT was centralized using 70 kg to facilitate the integration of adult data

Figure 6 Goodness-of-Fit – Final Population PK Model of Burosumab in Patients with XLH



Green circles= infants with XLH; Red circles = children with XLH, Black circles = adults with XLH.
Conc = Concentration; IDENT= Line of identity; LOESS = Locally weighted scatter plot smoothing; PK = Pharmacokinetic; XLH= X-linked hypophosphatemia
Note 1: Observed concentrations vs. individual and population predicted concentrations are presented on log scales in the upper left and upper central plots, and in linear scales in the lower left and lower central plots.
Note 2: Age categories are infants (1 month-2 years old), children (2- 12 years old) and adults (>17 years old)

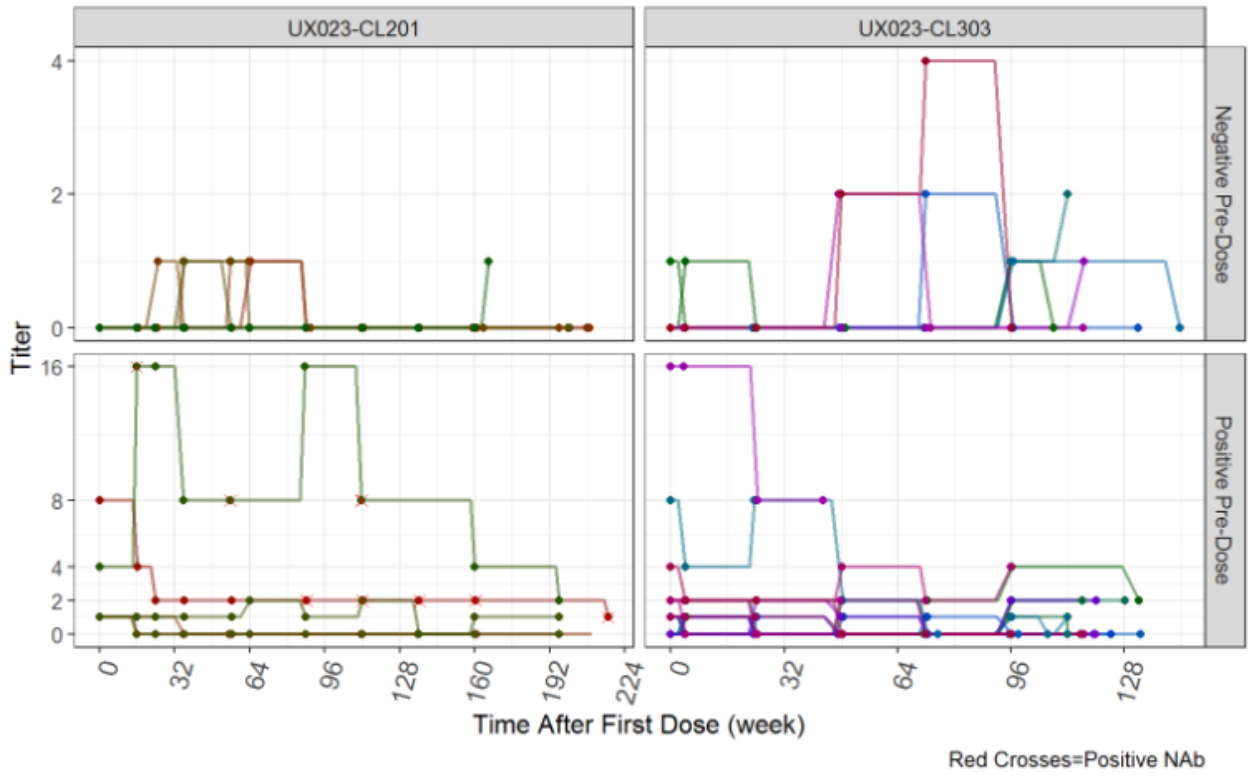
Figure 7 Visual Predictive Check for Subcutaneous Administration of Burosumab in Patients with XLH



Effect of Anti-drug Antibodies on Burosumab PK

The impact of immunogenicity, as assessed in the improved ADA assay, was evaluated by incorporating the ADA data into integrated population PK model burosumab. The dataset set used in the population PK analysis, presented above, was updated with the improved immunogenicity data in Studies UX023-CL205, UX023-CL201 and UX203-CL303. A total of 48 unique subjects tested positive for ADA at any time during the studies including at pretreatment baseline. Among these subjects, 15 subjects developed de novo ADA induced by burosumab after their first exposures to burosumab treatment, and 33 subjects had positive ADA status before receiving their first dose of burosumab, likely reflecting the presence of pre-existing cross-reactive antibodies. Figure 4 represents individual profiles of titer levels in patients with at least one positive ADA samples stratified by study and status of ADA at baseline before the first dose of burosumab.

Figure 3 Individual Time Profiles of Titer Levels of Anti-Burosumab Antibody in Patients with XLH in Studies UX023-CL201 and U023-CL303



NAb= Neutralizing antibody; XLH= X-linked hypophosphatemia
Note= Each color represents profile in one subject

The impact of ADA status on burosumab PK was evaluated in the population model using 3 different methods of analysis (ie, treating ADA as time-invariant, time-variant or time-latent covariate). In the combined 48 study subjects with at least 1 positive ADA sample during any time of studies, the mean values of CL/F (0.315 L/day) and V/F (6.81 L) were moderately greater than the corresponding values for the 229 subjects tested negative in ADA status (ie, 23% and 5.3% higher in CL/F and V/F, respectively). The difference between the ADA positive and negative groups further decreased after normalising individual values with the respective body weight (ie, 16.3% and 1.8% higher in weight-adjusted CL/F and V/F, respectively). In the subgroup analysis, the 15 subjects who tested ADA positive after the first burosumab administration had mean CL/F and V/F values similar to those of the 221 subjects who maintained negative ADA status during the clinical studies, suggesting seroconversion of ADA status had no effect on burosumab disposition.

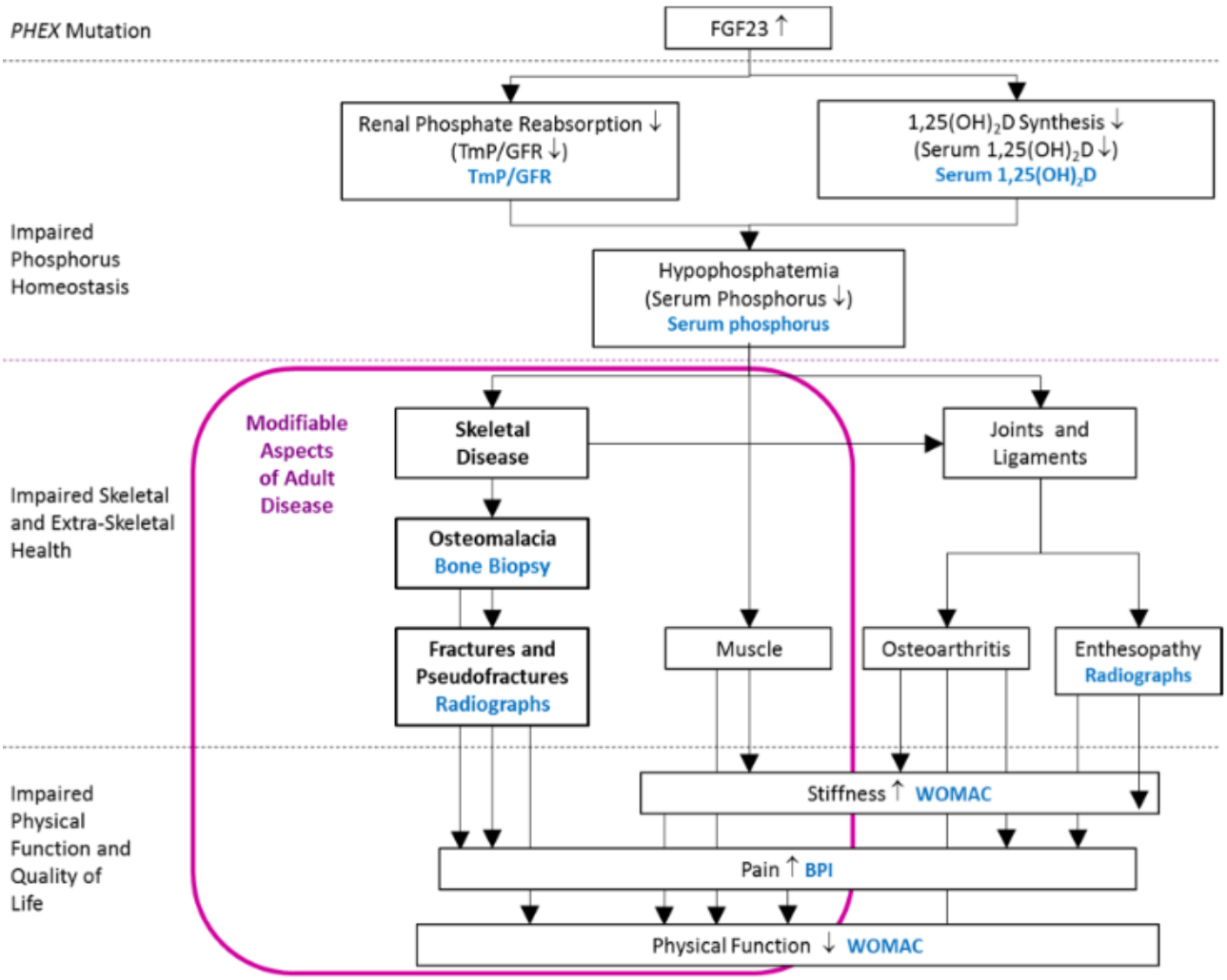
2.3.3. Pharmacodynamics

XLH is a rare, genetic disorder characterised by hypophosphatemia driven by excess fibroblast growth factor 23 (FGF23). FGF23 is a specific regulator of serum phosphorus; its major function is to reduce serum phosphorus levels by inhibiting renal proximal tubular phosphate reabsorption. FGF23 also decreases serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] levels by inhibiting 1-alpha-hydroxylase activity in the kidney, thereby decreasing intestinal absorption of phosphate and calcium. Both actions by FGF23 on the tubular reabsorption and intestinal absorption of phosphate via vitamin D metabolism decrease serum phosphorus levels.

Mechanism of action

Burosumab (Crysvita) is a recombinant fully human IgG1 monoclonal antibody that binds to and inhibits the excessive biological activity of FGF23. By inhibiting FGF23, burosumab is intended to restore tubular reabsorption of phosphate from the kidney and increase the production of $1,25(OH)_2D$, which enhances intestinal absorption of calcium and phosphate. Together, these actions improve serum phosphorus levels and bone mineralisation. XLH disease characteristics are summarised in Figure 5.

Figure 4: XLH Adult Disease Characteristics and Associated Endpoints



Blue text indicates associated endpoints assessed in the adult clinical development programme for burosumab. Note that assessments of mobility (the Six-minute Walk Test and Timed Up and Go test), which can be affected by multiple XLH disease characteristics, also were included as endpoints in adult studies. BPI = Brief Pain Inventory; FGF23 = fibroblast growth factor 23; 1,25(OH)2D = 1,25-dihydroxyvitamin D; PHEX = phosphate-regulating gene with homologies to endopeptidases on the X chromosome; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; XLH = X-linked hypophosphataemia

Primary and secondary pharmacology

As the pharmacodynamic marker serum phosphorus is the primary endpoint in the main adult clinical study UX023-CL303, the effect of burosumab on pharmacodynamics is discussed in the Clinical efficacy section.

2.3.4. PK/PD modelling

The population PK/PD analysis was based on simulated burosumab PK profiles in individual subjects using the original PK model and time-matched, baseline-subtracted serum phosphate level as the PD endpoint. Table 12 summarises the number of individual data points of serum phosphorus levels stratified by the age group available for the development of the population PK/PD model in subjects with XLH. Overall, a total of 6047 measurable concentrations of serum phosphorus were available for the development of the population PK/PD model in subjects with XLH, which is approximately 2-fold the number of PK samples included in the population PK analysis (Table 6). The serum phosphorus concentrations collected in the paediatric patients represented ~33% of the overall PD dataset of the PK/PD analysis. The results from the combination of data from the 7 studies in the original modelling and as well as the results using data from the 9 studies are presented below.

Table 10 Number of Serum Phosphorus Samples Available for the Population PK/PD Modelling

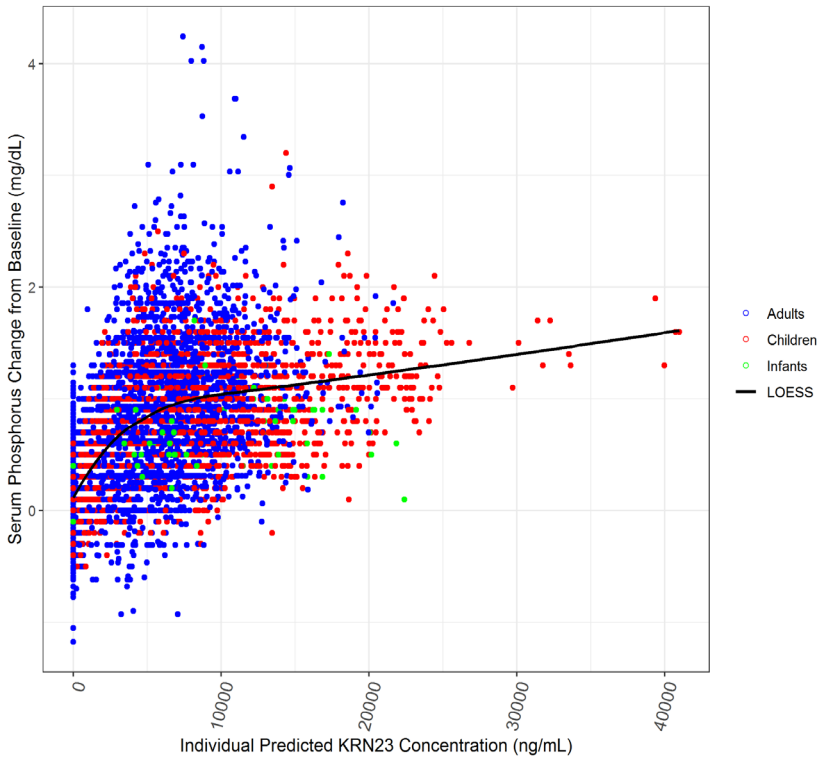
PD Samples	N (% of the overall)			
	Infants (1 month - 2 years old)	Children (2 - 12 years old)	Adults (>17 years old)	Overall
Include	74 (1.2%)	1916 (31.7%)	4057* (67.1%)	6047 (100%)

* No PD data was available for Study KRN23-US-02
N = Number of samples; PD = Pharmacodynamic; PK= Pharmacokinetic; XLH= X-linked hypophosphatemia.

During the trials, serum phosphorus levels were measured more frequently than burosumab concentrations. In order to retain all observed serum phosphorus data and allow a good estimation of the effect of time on the PK/PD relationship, serum phosphorus concentrations were paired with their time-matched simulation of PK concentrations. Individual PK parameters derived with the final population PK model of burosumab and the actual dosing history were used to simulate burosumab concentrations (simCKRN23) to pair with the observed phosphorus levels.

Figure 6 present the relationship between the serum phosphorus change from baseline and individual predicted burosumab concentrations. These figures show that the Emax of burosumab on serum phosphate change from baseline is approximately between 1-2 mg/dL and half of the maximum effect is observed around burosumab concentrations of ~ 5000 ng/mL. The PD effect appears to approach saturation at the burosumab concentration threshold of ~10,000 ng/mL.

Figure 5 Relationship between Serum Phosphorus Change from Baseline and Individual Predicted Concentrations of Burosumab in Adult and Paediatric Subjects with XLH – Based on 9 Studies



A standard, sigmoidal Emax model was used to describe the observed serum phosphate responses following various regimens of burosumab SC treatment. A moderate but statistically significant effect of body weight on baseline (E0) and maximal (Emax) were incorporated for improved model fitting as well as physiological plausibility and clinical observation. These observations included lower serum phosphorus level with increased age in normal subjects, and the few cases of hyperphosphataemia only being observed in adult XLH subjects treated with burosumab, which supports the selection of an Emax model. The original PK/PD model was presented in the initial MAA. Table 13 and Table 14 summarise the typical population PD parameter values estimated from the original and updated model, respectively.

Using the original integrated PK and PK/PD modelling, the estimated typical value of EC50 was 5783 ng/mL, which is independent of subject's age, body weight or the time on burosumab treatment. The updated model has lower estimates for EC50 (4606 ng/mL) and Emax (1.65 [mg/dL]/[ng/mL]). Using the previously predicted exposures and the new model estimates, the estimated percentage of Emax would be similar to the previous estimates. The modelling results are consistent with observed clinical efficacy in the paediatric and adult XLH trials and support the recommended dosing frequencies of Q2W and Q4W in the two populations respectively.

Table 11 Summary of Estimated Burosumab Population Typical PD Parameters in Adult and Paediatric XLH Patients – Original Model

Parameters		Typical Values (RSE(%))	BSV(%)	Shrinkage
PD Parameters	E0 (mg/dL)	2.05 (1.1%)	12.1%	16.0%
	EC_{50} (ng/mL)	5783 (10.5%)		
	Gam	0.925 (6.9%)	50.0%	40.6%
	E_{max} ([mg/dL]/[ng/mL])	1.92 (5.9%)	37.6%	16.3%
Covariate on E0	$(WT/70)^{effect}$	-0.14 (-11.3%)		
Covariate on E_{max}	$(WT/70)^{effect}$	0.28 (23.7%)		
Error Model	Additive error (mg/dL)	0.34 (2.0%)		

BSV = between subject variability; E0= baseline serum phosphorus; EC_{50}= simulated serum burosumab concentration to reach 50% of maximal effect; E_{max} = maximum effect; gam = Hill coefficient (Gamma); nGam = individual random effect of Gamma; PD= pharmacodynamic; PK= pharmacokinetic; RSE= relative standard error; $simC_{KRN23}$= simulated burosumab concentration; WT = bodyweight.

Note: The model equation is: $Phos=E0+(E_{max}.simC_{KRN23}^{Gam})/(EC_{50}^{Gam}+simC_{KRN23}^{Gam})$.

Source: Report ULTR-CSC-105 Table 14.

Table 12 Summary of Estimated Burosumab Population Typical PD Parameters in Adult and Paediatric XLH Patients – Updated Model

Parameters		Typical Values (RSE)	BSV (Shrinkage)
PK/PD Parameters	E0 (mg/dL)	2.03 (1.07%)	12.0% (11.2%)
	EC_{50} (ng/mL)	4606 (12.7%)	122.2% (37.5%)
	Gam	1 (Fixed)	
	E_{max} ([mg/dL]/[ng/mL])	1.65 (5.73%)	54.6% (28.9%)
Covariate on E0	(WT/70)effect	-0.136 (8.90%)	
Covariate on E_{max}	(WT/70)effect	0.199 (21.0%)	
Residual errors	Proportional error (%)	13.1 (1.80%)	

BSV = between subject variability; E0 = baseline serum phosphorus; EC_{50} = simulated serum burosumab concentration to reach 50% of maximal effect; E_{max} = maximum effect; Gam = Hill coefficient (Gamma); PD = pharmacodynamic; PK = pharmacokinetic; RSE = relative standard error; $simC_{KRN23}$ = simulated burosumab concentration; XLH = X-linked hypophosphatemia.

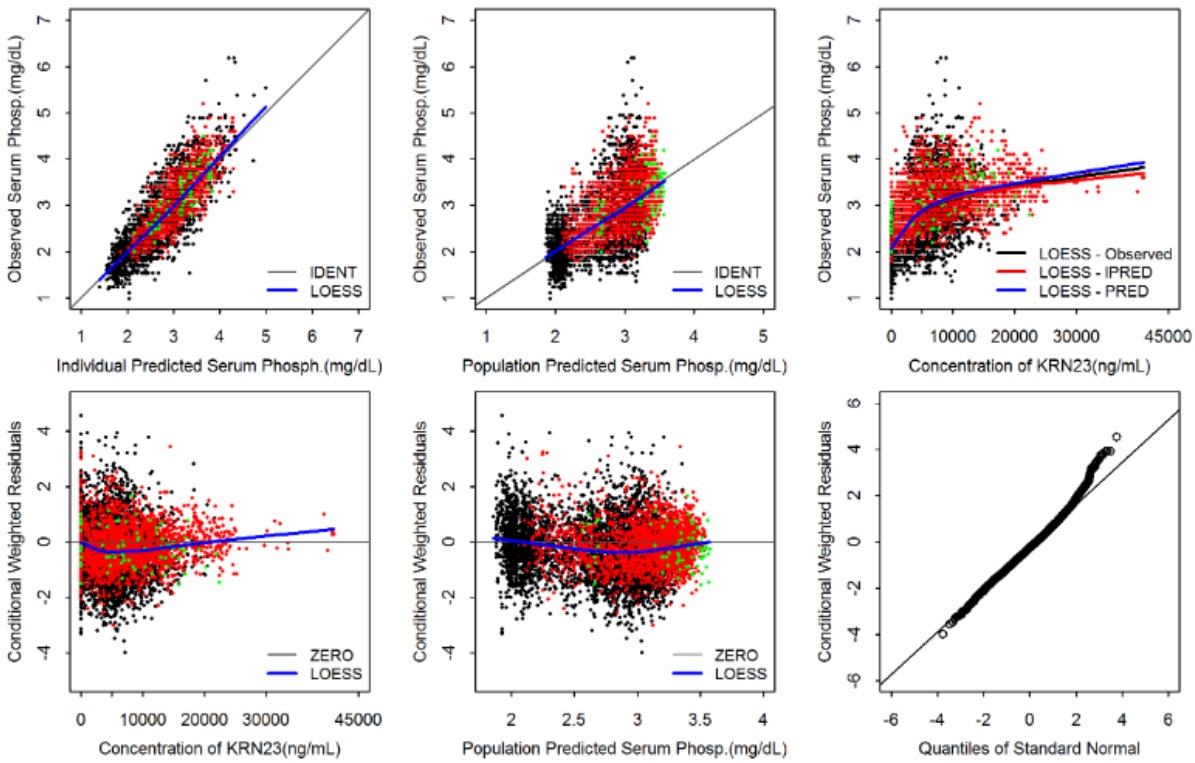
Note 1: The model equation is: $Phos=E0+(E_{max}\times simC_{KRN23}^{Gam})/(EC_{50}^{Gam}+simC_{KRN23}^{Gam})$.

Note 2: Effect of baseline WT was centralised using 70 kg to facilitate the integration of adult data.

Source: Report ULTR-CSC-106 Table 9.

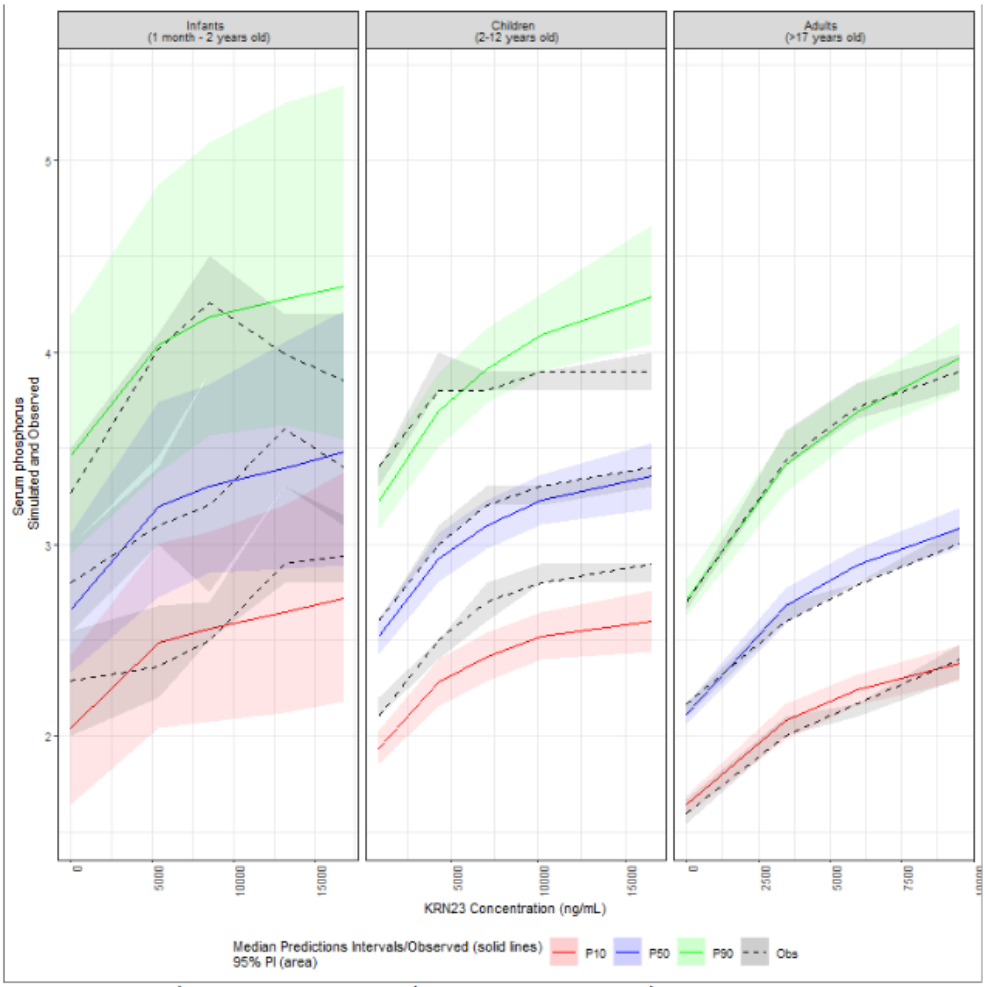
The PK/PD model was evaluated through goodness-of-fit diagnostics and visual predictive checks, as displayed in Figure 7 and Figure 8, respectively.

Figure 6 Goodness-of-Fit of the Updated Population PK/PD Model for Serum Phosphorus-Burosumab Relationship in Patients with XLH



Green circles= infants with XLH; Red circles = children with XLH, Black circles = adults with XLH.
IDENT= Line of identity; IPRED = Individual predicted phosphorus; LOESS = Locally weighted scatter plot smoothing; PD = Pharmacodynamic; Phos= Phosphorus; PK= Pharmacokinetic; PRED = Population predicted serum phosphorus; XLH= X-linked hypophosphatemia.
Note: Age categories are infants (1 month-2 years old), children (2- 12 years old) and adults (>17 years old)

Figure 7 Visual Predictive Check of Burosumab Concentration/Serum Phosphorus Relationship for SC Administration of Burosumab in Patients with XLH



Obs= Observations; P10= 10th percentile; P50= 50th percentile; P90= 90th percentiles; PD = Pharmacodynamic; PK= Pharmacokinetic; PI= Prediction interval; XLH= X-linked hypophosphatemia.
Note 1: Uncertainty on observations was determined by re-sampling the observations within each bin (N=1000) and model predictions were based on 1000 replicates of the dataset.
Note 2: PD data were regrouped into 5 bins with same number of samples by bin by population.

***Population PK/PD modelling of serum phosphorus levels* (Report ULTR-PMX-1280)**

The number of individual data points of serum phosphorus levels stratified by the age group available for the development of the population PK/PD model in subjects with XLH are presented in Table 7.

Table 7 Number of Serum Phosphorus Samples Available for the Population PK/PD Modeling

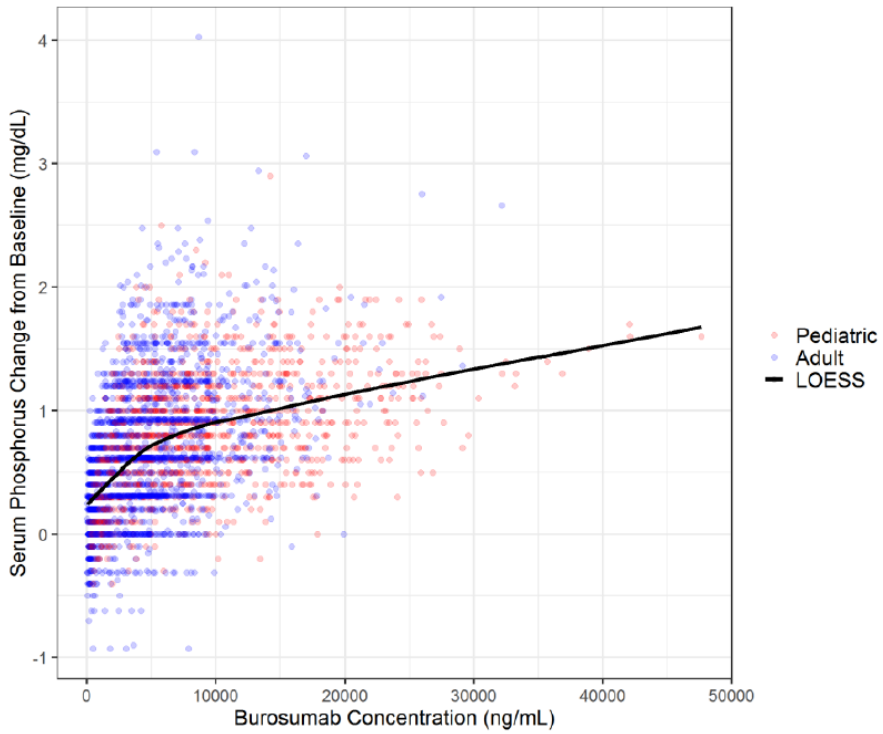
PD Samples	N (% of the overall)			
	Infants (1 - 2 years old at the 1st dose treatment)	Children (2 - 12 years old)	Adults (>17 years old)	Overall
Include	74 (0.99 %)	2307 (30.9 %)	5096 (68.2 %)	7477 (100 %)*

* No PD data was available for Study KRN23-US-02
N = Number of samples; PD = Pharmacodynamic; PK= Pharmacokinetic; XLH= X-linked hypophosphatemia.

Individual PK parameters derived with the final population PK model and the actual dosing history were used to simulate burosumab concentrations ($simC_{KRN23}$) to pair with the observed phosphorus levels.

The relationship between individual predicted burosumab concentrations and serum phosphorus change from baseline observed in the 269 patients included in the population PK/PD analysis is presented in Figure 8. This figure shows that the Emax of change in serum phosphorus from burosumab treatment is greater than 1 mg/dL and half of the maximum effect is observed around burosumab concentrations of 5000 ng/mL, i.e., the EC50 value. Approximately homogeneous distributions of the adult and paediatric data points were observed with slightly higher maximum effect in adults.

Figure 8 Relationship between Serum Phosphorus Change from Baseline and Individual Predicted Concentrations of Burosumab in Patients with XLH



LOESS= Locally weighted scatter plot smoothing; XLH= X-linked hypophosphatemia
Note: Age categories are pediatrics (i.e., infants and children) and adults

The previous PK/PD model developed with data from paediatric and adult subjects with XLH (report ULTR-CSC-106) was used as a starting point to evaluate the relationship between burosumab and serum phosphorus concentrations in the current dataset including longer following-up in Studies UX023-CL201 and UC023-CL303. As with the previous model, the structural PK/PD parameters in the current model included E0, EC50, Emax, as well as BSV associated with these parameters. Hill coefficient (ɣ fixed to 1, 2 or estimated value), unexplained residual error models (i.e., proportional and mixed error models) and the time-varying WT effect on E0 and Emax were evaluated to determine the structural population PK model. The best structural model was obtained with WT effect on E0 only, with estimated value for the Hill coefficient and a mixed residual error model.

The inclusion of serum ALP on Emax resulted in a marked decrease in MOF value with a reduction of 2.0% of BSV on Emax. After incorporating WT on E0 and ALP on Emax as a structural model covariate, no other significant trends were detected with other potential covariates.

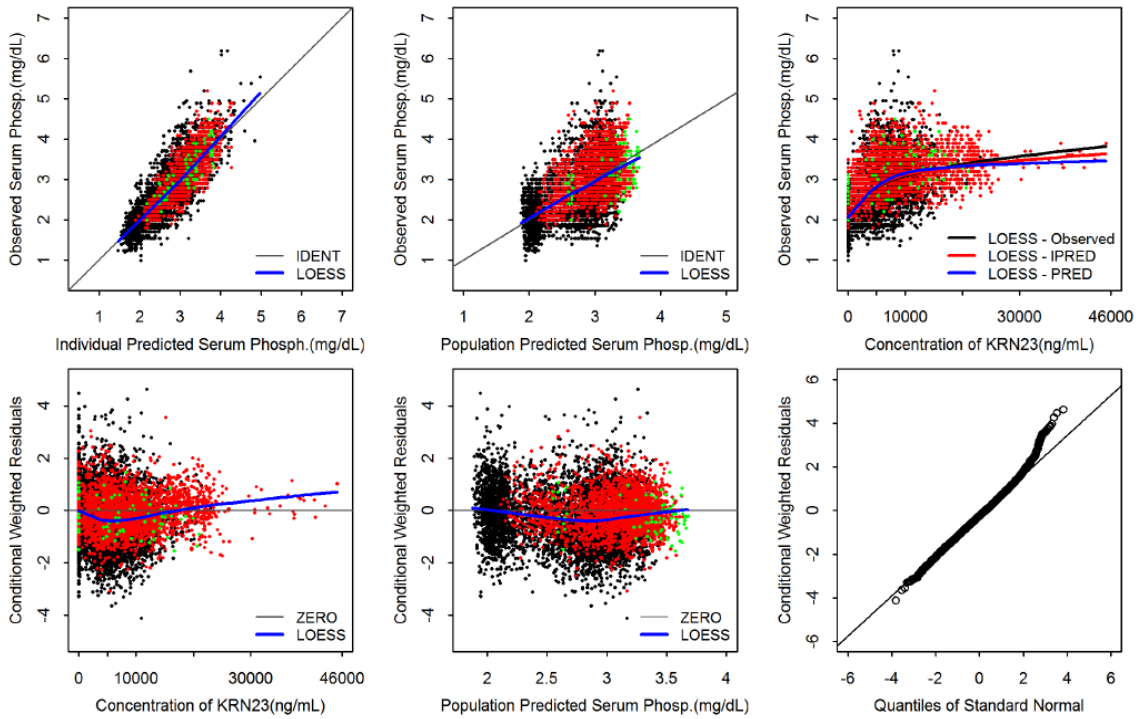
The point estimates with associated uncertainties for the typical population values of PK/PD parameters derived from the final model are presented in Table 10. Diagnostic plots for the final population PK/PD model are presented in Figure 11. VPC plots stratified by age population are shown in Figure 12.

Table 10 Typical Values of the Final Population PK/PD Model of Serum Phosphorus in Patients with XLH

	Parameters	Typical Values (RSE%)	BSV(%)	Shrinkage
PD parameters	E0 (mg/dL)	2.05 (1.06%)	11.7%	11.5%
	EC_{50} (ng/mL)	3819 (10.2%)	87.6%	25.2%
	Hill coefficient	1.53 (9.0%)		
	E_{max} (mg/dL)	1.30 (5.2%)	45.5%	22.7%
Covariate on E0	$(WT/70)^{effect}$	-0.128 (9.7%)		
Covariate on E_{max}	$(ALP/150)^{effect}$	-0.110 (30.6%)		
Residual errors	Proportional error (%)	13.2 (1.84%)		

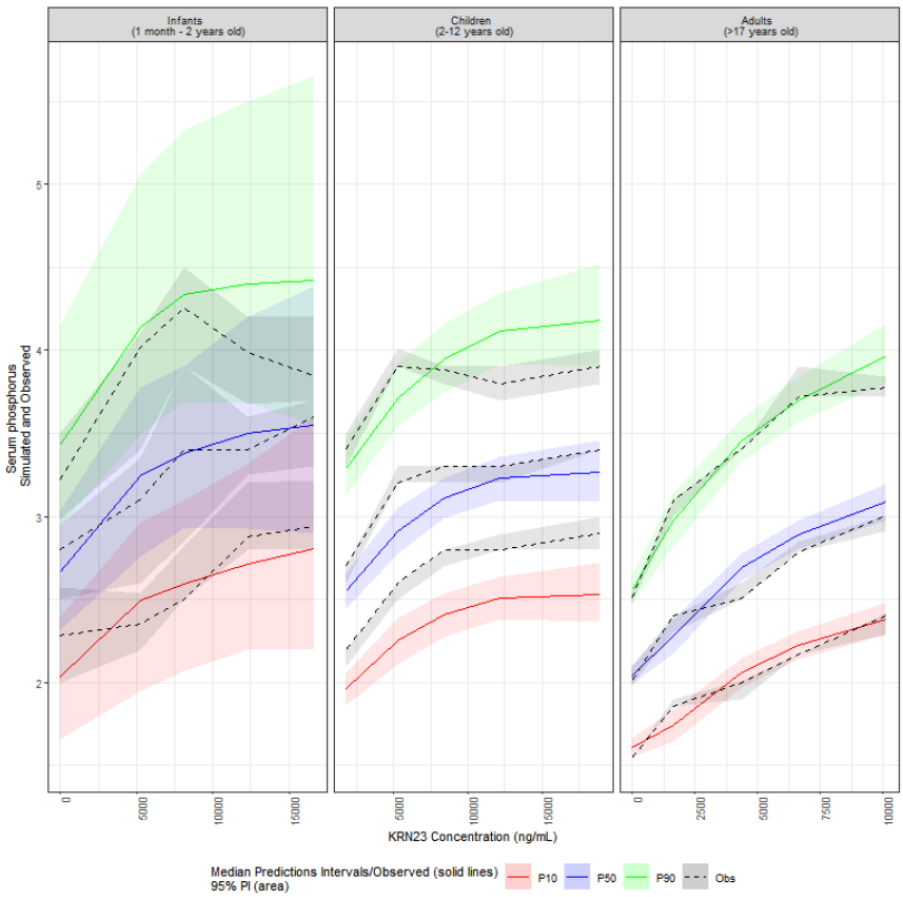
ALP= Alkaline phosphatase (U/L); BSV= Between subject variability; CI= Confidence interval; E0= Baseline serum phosphorus; EC_{50}= Simulated serum burosumab concentration to reach 50% of maximal effect; E_{max}= Maximum effect; Gam = Hill coefficient; PD= Pharmacodynamic; PK= Pharmacokinetic; RSE= Relative standard error; $simC_{Burosumab}$ = Simulated Burosumab concentration; WT = body weight.
Note 1: The model equation is: $Phos=E0+(Emax \times simC_{Burosumab}{}^{Gam})/(EC50^{Gam}+ simC_{Burosumab}{}^{Gam})$

Figure 11 Goodness-of-Fit of the Final Population PK/PD Model for Serum Phosphorus-Burosumab Relationship in Patients with XLH



Green circles= infants with XLH; Red circles = children with XLH, Black circles = adults with XLH.
IDENT= Line of identity; IPRED = Individual predicted phosphorus; LOESS = Locally weighted scatter plot smoothing; PD = Pharmacodynamic; Phos= Phosphorus; PK= Pharmacokinetic; PRED = Population predicted serum phosphorus; XLH= X-linked hypophosphatemia.
Note: Age categories are infants (1 month-2 years old), children (2- 12 years old) and adults (>17 years old)

Figure 12 Visual Predictive Check of Burosumab Concentration/Serum Phosphorus Relationship for SC Administration of Burosumab in Patients with XLH



Obs= Observations; P10= 10th percentile; P50= 50th percentile; P90= 90th percentiles; PD = Pharmacodynamic; PK= Pharmacokinetic; PI= Prediction interval; XLH= X-linked hypophosphatemia.
Note 1: Uncertainty on observations was determined by re-sampling the observations within each bin (N=1000) and model predictions were based on 1000 replicates of the dataset.
Note 2: PD data were regrouped into 5 bins with same number of samples by bin by population.

A statistically significant negative correlation was observed between serum phosphorus at baseline and time-varying WT, with point estimate of -0.128. This is consistent with inverse relationship between serum phosphorus level and age in healthy children and the general understanding that higher phosphate metabolism is needed to support faster bone growth in younger population. A statistically significant negative correlation was observed between Emax and serum ALP with point estimate of -0.110. The average trough burosumab concentration of 15,000 ng/mL observed in Studies UX023-CL201 would result in ~90.0% of Emax, which corresponds to serum phosphorus levels of 3.62 mg/dL and 3.38 mg/dL based on the median values of WT and ALP for infants and children, respectively.

Effect of Anti-drug Antibodies on Burosumab PK/PD

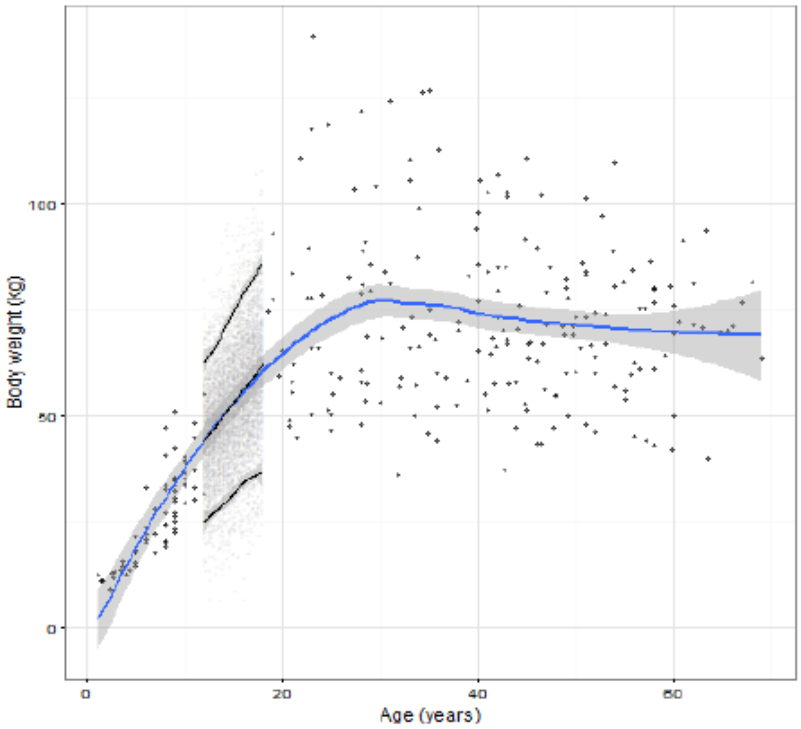
The impact of immunogenicity, as assessed in the improved ADA assay, was evaluated by incorporating the ADA data into integrated population PK model burosumab. The dataset set used in the population PK analysis, presented above, was updated with the improved immunogenicity data in Studies UX023-CL205, UX023-CL201 and UX203-CL303. A total of 48 unique subjects tested positive for ADA at any time during the studies including at pretreatment baseline. Among these subjects, 15 subjects developed de novo ADA induced by burosumab after their first exposures to burosumab treatment, and 33 subjects had positive ADA status before receiving their first dose of burosumab, likely reflecting the presence of pre-existing cross-reactive antibodies.

The posterior Bayes parameters of EC50 and Emax obtained in the 48 subjects positive for ADA were moderately higher than those obtained in subjects with negative ADA status (i.e., mean values were 25% and 15% higher, respectively), and the magnitude of these differences are unlikely to be clinically important. In the subgroup analysis, the 15 subjects who tested positive for ADA after the first burosumab administration had essentially identical mean EC50 and Emax values compared with the 221 subjects who maintained negative ADA status during the clinical studies, suggesting seroconversion of ADA status had no effect on burosumab PD.

Simulations to Support Dosing Regimens of Burosumab XLH Subjects

The paediatric XLH subjects enrolled in Studies UX023-CL201 and UX023-CL205 were aged 5-12 years old and 1-4 years old at screening, respectively, and did not include the adolescent population (age range of 13-17 years old). The unified PK and PK/PD models are based on observed PK and PD data in both adult and paediatric XLH subjects and should be applicable to the adolescent age group; therefore, modelling and simulations is used to support the dose regimen for this age population of XLH patients. It is noted that body weight is the only structural covariate incorporated in the population PK and PK/PD models. Therefore, body weights of adolescent subjects with XLH were modeled using a General Additive Model for Location, Scale and Shape (GAMLSS) based on the actual baseline body weight distributions observed in paediatric (1-<12 years old) and adult (18-<69 years old) subjects included in the population PK and PK/PD analyses. Simulations of the GAMLSS model were then performed by randomly generating body weight values in 100,000 adolescent XLH subjects from 12-17 years of age, inclusively. The distribution of body weight in adolescent XLH populations is presented in Figure 9. To avoid outliers, body weight values included in the 90% CI of generated body weight were retained in the virtual population of adolescents.

Figure 8 Distribution of Body Weight in the Virtual Populations and in the Population Included in the Population PK and PK/PD Analyses in Subjects with XLH



PK = pharmacokinetic; PD = pharmacodynamic; XLH = X-linked hypophosphatemia.

Note: Black dots represent the observed body weight in the population included in the analyses, blue line and gray area represent the LOESS line on observed body weights with 95%CI.

Gray dots represent the distribution of body weights generated using GAMLSS model, black lines represent LOESS on the overall and the 5th and 95th percentile intervals.

Source: Report ULTR-CSC-105, Figure 16.

The original population PK/PD model was used to simulate exposure to burosumab and serum phosphorous for the two dosing regimens recommended for paediatrics and adults, i.e., 0.8 mg/kg Q2W and 1.0 mg/kg Q4W, respectively. A virtual XLH adolescent population was simulated by sampling the body weight of subjects included in the virtual adolescent population (n = ~1000 XLH subjects per dosing regimen). The time-profiles of burosumab, serum phosphorus (absolute and change from baseline) at steady-state were derived for a duration of four weeks.

Descriptive statistics of minimum, average and maximum levels of burosumab concentrations, serum phosphorus and change from baseline from the simulations are presented in Table 15.

Table 13 Descriptive Statistics of Predicted PK and PD in XLH Adolescent Subjects (Dose Levels Rounded to the Nearest 10 mg with Maximum of 90 mg)

Analyte Concentration	PK Exposure	Geometric Mean (Geometric CV%) Median [5th-95th percentiles]	
		0.8 mg/kg Q2W	1.0 mg/kg Q4W
Serum burosumab	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]
Serum Phosphorus	C_{min} (mg/dL)	3.21(18%) 3.18[2.29-4.54]	2.95(21%) 2.93[2.07-4.27]
	C_{avg} (mg/dL)	3.32(16%) 3.29[2.48-4.65]	3.17(17%) 3.12[2.33-4.52]
	C_{max} (mg/dL)	3.38(16%) 3.34[2.57-4.72]	3.33(16%) 3.30[2.51-4.70]
Serum Phosphorus Change from Baseline	C_{min} (mg/dL)	0.903(-812%) 1.03[0.215-2.37]	0.535(-241%) 0.755[0.0395-2.12]
	C_{avg} (mg/dL)	1.07(776%) 1.11[0.406-2.46]	0.905(-629%) 0.941[0.325-2.32]
	C_{max} (mg/dL)	1.15(354%) 1.17[0.509-2.53]	1.09(630%) 1.10[0.477-2.49]

C_{avg}= average concentration; C_{max}= maximum concentration; C_{min} = minimum concentration; CV= coefficient of variation; PD = pharmacodynamics; PK= pharmacokinetic; Q2W= biweekly, once every two weeks; Q4W= monthly, once every four weeks; XLH = X-linked hypophosphatemia.
Source: Report ULTR-CSC-105, Table 15.

For 0.8 mg/kg Q2W and 1.0 mg/kg Q4W dosing regimens, there were ~ 51% and 65% of the simulated minimum of serum phosphorus levels lower than 3.2 mg/dL (the lower bound of normal serum phosphate range), respectively, whereas only 2.9% and 3.3% of the simulated maximum of serum phosphorus levels were higher than 5.0 mg/dL (the upper bound of normal serum phosphate range), respectively. In clinical practice, burosumab administration is to be titrated to normal phosphate range. 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, the lower bound of normal range, it is recommended that the adolescent XLH patients should receive the same dose for other paediatric patients aged 1-12 years old, burosumab 0.8 mg/kg Q2W.

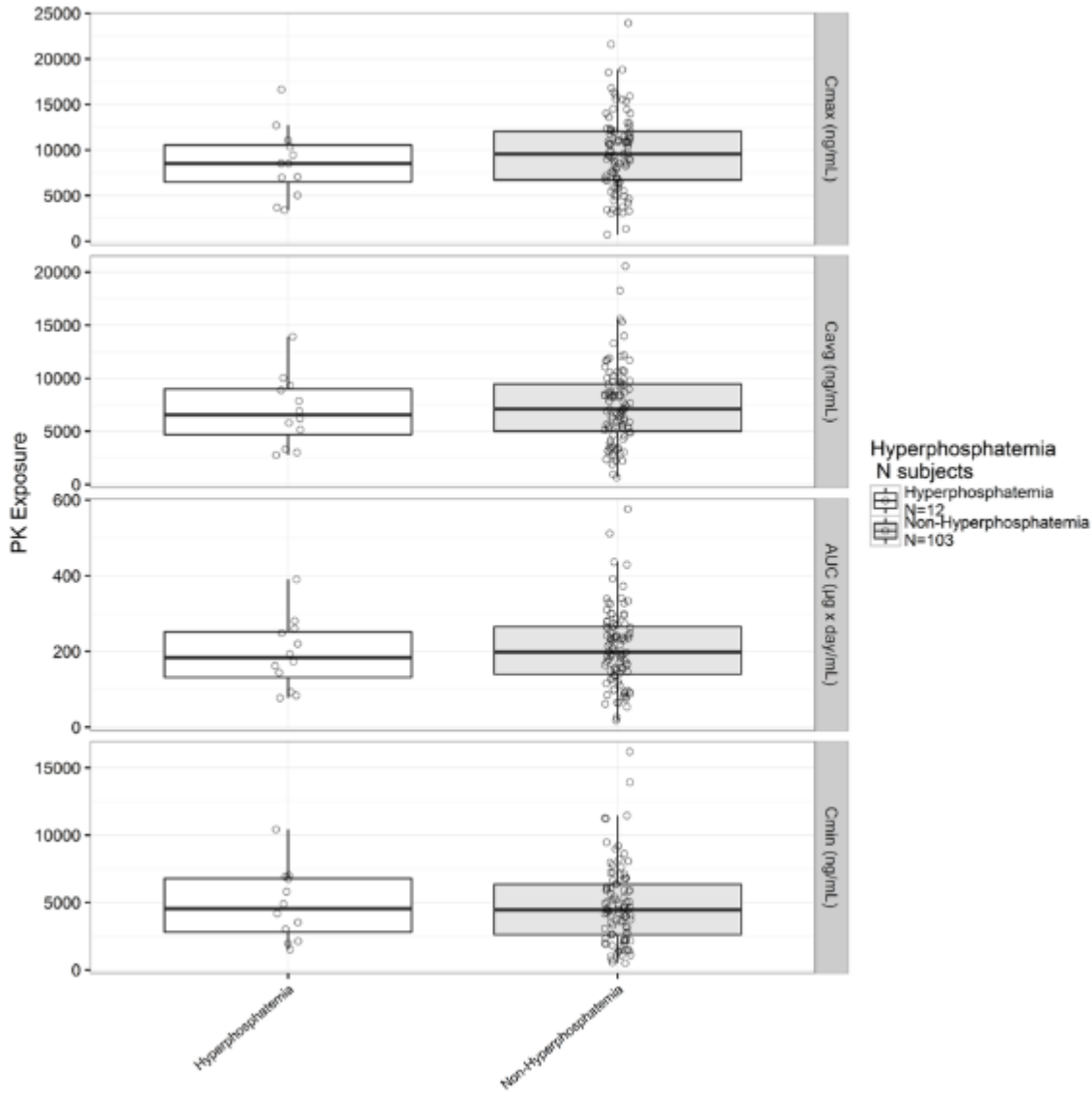
Exposure Response (Efficacy and Safety) Relationship

Exposure-Response (ER) analysis for efficacy has been conducted for serum phosphorus change in the form of population PK/PD analysis, described above.

ER analysis for safety was evaluated for the events of hyperphosphataemia. For the purpose of this analysis, hyperphosphataemia was defined as observation of serum phosphorus level >4.5 mg/dL from one or more lab measurements. No hyperphosphataemia was observed in any paediatric XLH subjects. Out of the 12 adult XLH subjects (11 from Study UX023-CL303 and 1 from Study UX023-CL203) who had at least 1 observation of hyperphosphataemia, 5 subjects had serum phosphorus level >4.5 mg/dL from repeat measurements. Burosumab serum exposures were compared between these 12 subjects versus

those from adult XLH subjects who did not have hyperphosphataemia. PK exposure (Cmax, Cmin and AUC) distributions demonstrated overlap between the two groups with similar median values (Figure 10); hence, the occurrence of hyperphosphataemia did not have any apparent association with burosumab serum exposures.

Figure 9 Relationship between Hyperphosphataemia and PK Exposure Levels of Burosumab in Adult Patients with XLH



Footnotes for previous figure:
AUC = area under the concentration-time curve over one dosing interval; Cavg = average concentration; Cmax = maximum concentration; Cmin = minimum concentration; N = number of subjects; PK = pharmacokinetic; XLH = X-linked hypophosphatemia.
Note 1: For patients enrolled in more than one study, the posterior Bayes parameters derived in the 1st enrolled trial were retained.
Note 2: Only adults are presented. Source: Report ULTR-CSC-105, Figure 9.

2.3.5. Discussion on clinical pharmacology

An improved bioanalysis method for the detection of anti-burosumab antibodies have been developed. The MAH has provided evidence that the cutpoint and subsequent analysis are adequate.

The pharmacokinetics of burosumab was reported in the initiall MAA. For the purpose of further describing the burosumab PK in the adult population, an updated population PK integrated analysis has been presented with the inclusion of additional data from studies UX023-CL303, UX023-CL304, and paediatric

study UX023-CL301. Graphical comparison of the distributions of observed burosumab exposure, across all age groups, indicate that the adult population have a somewhat lower exposure compared to the paediatric population. This is expected, as the dose in adults is approximately halved compared to children.

The updated PK model displayed minor differences from the previously reported PK model, and hence the previously reported PK properties of burosumab withstand. The previously reported PK model was used for simulations to support the recommended dosing strategy.

In the population PK model, estimated allometric exponents for the body weight relationships were used. Although it is often recommended to use fixed theoretical exponents, the Applicant showed in the initial MAA that there were minor differences in the population predictions between estimated and fixed exponents, favouring the estimated values. Thus, estimated exponents were accepted.

The relationship between burosumab serum concentration and observed phosphorus levels was described with a direct effect Emax model. As in the initial MAA, time-matched simulated serum concentration levels were imputed where observed serum concentrations were missing. The original model was assessed in the MAA and only minor changes were made in the updated analysis, which are accepted. The analysis identified a large inter-individual variability in the EC50 value, i.e. the concentration to achieve 50% of the maximum effect. This finding supports the need for dose titration to achieve an adequate phosphorus level for all patients.

The predicted burosumab exposures between the children 2-12 years and the adolescent population are comparable, and the adult burosumab exposure ranges are decreased by half compared to the paediatric populations. This is expected as the dose is approximately halved going from 0.8 mg/kg Q2W to 1 mg/kg Q4W. According to the PKPD analysis, the serum phosphorus levels are similar across age groups with the proposed posology indicating that a switch from 0.8 mg/kg Q2W to 1 mg/kg QW4 would be acceptable.

With regard to the burosumab exposure range for patients >90 kg, the MAH has provided a comparison between the full adult XLH patient population and patients >90. Comparing the observed phosphorus levels there are minor differences between patients >90 kg and <90 kg. It should be noted, however, that only 9 patients weighed >90 kg. Although it would have been valuable to have the exposure ranges presented <90 kg and >90 kg, the phosphorus levels seem to indicate that no dose adjustment for patients >90 kg is warranted. The MAH has proposed a dosing regimen of 0.8 mg/kg Q2W in the adolescent patient population and a 1 mg/kg Q4W dosing regimen in the adult population. As indicated by the predictions from PKPD model, the average phosphorus levels will remain largely the same although with greater fluctuations. The predicted peak to trough serum exposure ratios in adolescents are 1.33-fold and 2.13-fold for the burosumab 0.8 mg/kg Q2W and burosumab 1.0 mg/kg Q4W regimens, respectively, which translates to ratios of 1.06-fold and 1.24-fold for the change from baseline of serum phosphorus, and 1.03-fold and 1.10-fold for serum phosphate for these regimens, respectively. The applicant argues that by the age of 18 years, the importance of the fluctuations is lower as bone growth and maturity begins to slow relative to the early adolescent development. The justification for the dose switch to the adult dose at 18 years of age is acceptable as the average phosphorus levels are largely maintained.

As the pharmacodynamic marker serum phosphorus is the primary endpoint in the main adult clinical study UX023-CL303, the effect of burosumab on pharmacodynamics is discussed in the Clinical efficacy section.

2.3.6. Conclusions on clinical pharmacology

Population PK and PK/PD analyses have been provided to support the dosing recommendations in the adolescent and adult populations. No major differences between the paediatric and adult populations were identified. The average phosphorus levels are largely similar across age and bodyweight, hence the proposed dosing recommendation is endorsed.

2.4. Clinical efficacy

The interventional studies of burosumab that contribute to the assessment of efficacy are listed in Table 1 (paediatric population) and Table 2 (adult population).

The efficacy of burosumab in adults with XLH was evaluated in two Phase 3 studies (UX023-CL303 and UX023-CL304), two Phase 1/2 adult studies (KRN23-INT-001 and KRN23-INT-002), and one long-term Phase 2b extension, Study UX023-CL203, for which a Week 48 analysis has been completed.

Study KRN23-INT-001 was the first multiple dose study in adult patients. Patients who satisfactorily completed this study could enter KRN23-INT-002. Patients from these studies entered the long-term extension study UX023-CL203.

The primary evidence of burosumab efficacy in adults with XLH comes from Study UX023-CL303. Supportive efficacy data are provided from Study UX023-CL304, Study UX023-CL203 and the two Phase 1/2 studies.

In the approved paediatric posology, burosumab is administered every second week (Q2W). The applicant has not explored a Q2W dosing in adult patients and has conducted all clinical studies with a Q4W administration.

Baseline demographic data for all studies are given in Table 16

*Table 14 Demographic and Baseline Characteristics: Repeat-dose Studies in **Adult XLH** (truncated by Assessor)*

	UX023-CL303			UX023-CL304	UX023-CL203	KRN23-INT-001/002 [b]	
	Double-blind Period (Week 0-24)		Total Burosumab [a]				Overall Burosumab [c]
	Placebo (N = 66)	Burosumab (N = 68)	(N = 134)	Burosumab (N = 14)	Burosumab (N = 20)	Burosumab (N = 28)	(N = 176)
Age (years)							
Mean (SD)	38.6 (12.76)	41.3 (11.58)	40.0 (12.20)	40.1 (8.72)	46.2 (12.91)	41.9 (13.83)	40.3 (12.20)
Median	35.4	41.9	41.2	39.4	50.0	41.5	41.0
Q1, Q3	28.5, 48.8	33.7, 49.4	29.0, 48.9	32.3, 49.6	39.0, 54.5	31.5, 52.5	30.0, 49.6
Min, Max	19, 66	20, 63	19, 66	25, 52	19, 66	19, 66	19, 66
Age Group (years) – n (%)							
≥18 to ≤50	54 (81.8%)	52 (76.5%)	106 (79.1%)	12 (85.7%)	10 (50.0%)	17 (60.7%)	135 (76.7%)
>50	12 (18.2%)	16 (23.5%)	28 (20.9%)	2 (14.3%)	10 (50.0%)	11 (39.3%)	41 (23.3%)
Sex – n (%)							
Male	23 (34.8%)	24 (35.3%)	47 (35.1%)	6 (42.9%)	6 (30.0%)	9 (32.1%)	62 (35.2%)
Female	43 (65.2%)	44 (64.7%)	87 (64.9%)	8 (57.1%)	14 (70.0%)	19 (67.9%)	114 (64.8%)
Race – n (%)							
White/ Caucasian	53 (80.3%)	55 (80.9%)	108 (80.6%)	9 (64.3%)	19 (95.0%)	27 (96.4%)	144 (81.8%)
Black or African American or African Caribbean	3 (4.5%)	0 (0%)	3 (2.2%)	1 (7.1%)	1 (5.0%)	1 (3.6%)	5 (2.8%)
Asian	9 (13.6%)	12 (17.6%)	21 (15.7%)	4 (28.6%)	0 (0%)	0 (0%)	25 (14.2%)
Other	1 (1.5%)	1 (1.5%)	2 (1.5%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)
Height (cm)							
Mean (SD)	152.7 (11.836)	152.2 (9.491)	152.4 (10.672)	150.4 (8.981)	147.3 (12.315)	150.3 (12.240)	151.9 (10.794)
Median	150.8	152.0	151.00	149.3	146.5	149.7	150.2
Q1, Q3	147.00, 162.00	146.00, 158.00	146.55, 158.20	144.00, 157.60	140.30, 155.65	143.10, 160.42	146.00, 158.40
Min, Max	120.6, 175.0	126.2, 176.0	120.6, 176.0	135.0, 165.0	121.9, 170.2	121.9, 170.2	120.6, 176.0
Body Mass Index (kg/m2)							
Mean (SD)	30.6 (7.790)	30.0 (7.480)	30.3 (7.611)	30.8 (8.470)	36.7 (11.505)	34.2 (10.958)	30.9 (8.367)
Median	30.2	29.5	29.8	30.0	35.9	31.4	30.0
Q1, Q3	25.50, 34.00	24.90, 33.10	25.15, 33.20	23.56, 33.09	29.95, 38.80	25.65, 38.40	25.30, 34.00
Min, Max	17, 59	20, 65	17, 65	22, 54	20, 68	20, 68	17, 68
Serum phosphorus (mg/dL)							
Mean (SD)	1.9 (0.316)	2.0 (0.304)	2.0 (0.314)	2.2 (0.396)	1.9 (0.367)	1.9 (0.326)	2.0 (0.331)
Median	1.9	2.0	2.0	2.3	1.9	1.9	2.0
Q1, Q3	1.70, 2.20	1.90, 2.20	1.80, 2.20	2.10, 2.40	1.70, 2.15	1.70, 2.10	1.80, 2.20
Min, Max	1, 3	1, 3	1, 3	1, 3	1, 3	1, 3	1, 3

a: The total burosumab column under UX023-CL303 includes all subjects who ever received any dose of burosumab in Study UX023-CL303. The length of burosumab treatment varies as it includes both subjects randomised to receive burosumab from baseline and subjects randomised to placebo who crossed over to receive burosumab at Week 24.
b: Includes subjects who participated in KRN23-INT-001 only, and subjects who participated in both KRN23-INT-001 and KRN23-INT-002. Twenty of those 28 subjects participated in Study UX023-CL203.
c: The overall burosumab group includes all subjects that have received burosumab in the adult repeat-dose XLH studies, including Study UX023-CL303 subjects randomised to placebo once they crossed over to burosumab. The unique number of subjects in this group is 175; however, 1 subject who enrolled in both KRN23-INT-001 and UX023-CL303 was analysed as 2 different subjects. Details are provided in Section 2.7.4.1.1.2.
The safety analysis set includes all subjects who received at least 1 dose of Investigational Product (burosumab or placebo). Data as of 08 Jun 2017 for ongoing Study UX023-CL303; data as of 08 Jun 2017 for ongoing Study UX023-CL304; data as of 08 Jun 2017 for ongoing Study UX023-CL203
Min = minimum; Max = maximum; N = total number of subjects who received at least 1 dose of Investigational Product (burosumab or placebo); Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

2.4.1. Dose response study(ies)

Both studies KRN23-INT-001 and KRN23-INT-002 were completed at the time of the initial MAA.

KRN23-INT-001

Study Title

A Phase 1/2, Open-Label, Repeat-Dose, Dose-Escalation Study of KRN23 in Adult Subjects with X-Linked Hypophosphatemia

Study Design

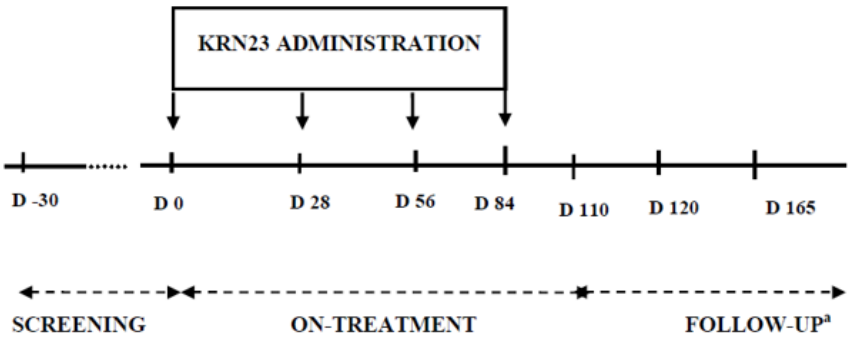
KRN23-INT-001 was a Phase 1/2, open-label, multiple-dose, dose-escalation study designed to assess the safety and efficacy of repeat-dose burosumab subcutaneous (SC) administration in adult subjects with XLH. The study also evaluated the effects of repeat-dose burosumab SC administration on pharmacodynamics (PD), pharmacokinetics (PK), immunogenicity, and HRQoL.

Eligible subjects were at least 18 years of age with a documented clinical diagnosis of XLH, intact FGF23 level >30 pg/mL, TmP/GFR <2.0 mg/dL and corrected serum calcium level <10.8 mg/dL [2.7 mmol/L].

A total of 32 adult subjects with XLH, of whom 18 had participated in single-dose Study KRN23-US-02, were assigned to treatment (30 subjects to burosumab in the open-label portion of the study and 2 subjects in the bone substudy [one to burosumab and one to placebo]). The KRN23-INT-001 bone sub-study was subsequently terminated due to slow accrual. As three subjects assigned to burosumab treatment were discontinued before receiving the first dose, 28 subjects were treated with burosumab in the study.

Each of the subjects was administered up to 4 SC doses of burosumab at 28-day intervals using a stepwise dose-escalation from 0.05 mg/kg → 0.1 mg/kg → 0.3 mg/kg →0.6 mg/kg that was guided by individual serum phosphorus levels using a dose-escalation algorithm and other safety observations. The treatment duration was up to 110 days (Figure 11).

Figure 10: Study design KRN23-INT-001



Baseline Characteristics

Please refer to Table 16

Exposure

A total of 28 subjects were treated with burosumab (27 in the open-label portion of the study and 1 in the bone substudy) and 1 subject was treated with placebo in the bone substudy. One subject (treated with burosumab) had a TEAE (injection site urticaria) that led to study drug discontinuation. This is further discussed in the Safety section.

The planned stepwise dose-escalation in study KRN23-INT-001 (0.05 mg/kg → 0.1 mg/kg → 0.3 mg/kg →0.6 mg/kg) was guided by individual serum phosphorus levels using a dose-escalation algorithm and other safety observations.
The mean ± standard deviation (SD) total dose of burosumab administered was 0.05 ± 0.00 mg/kg, 0.10 ± 0.01 mg/kg, 0.28 ± 0.06 mg/kg, and 0.48 ± 0.16 mg/kg during dosing intervals 1, 2, 3, and 4, respectively.

Most (92.9%, 26 subjects) subjects treated with KRN23 received all 4 doses of KRN23; 1 subject received 3 doses and 1 subject received 1 dose. The single subject in the placebo group in the bone substudy received all 4 doses of placebo.

Results

Primary Efficacy endpoint - Serum Phosphorus Levels

The number and percentage of subjects with maximum serum phosphorus levels ≤2.5 mg/dL [0.81 mmol/L], >2.5 to ≤3.5 mg/dL [0.81-1.13 mmol/L], >3.5 to ≤4.5 mg/dL [1.13-1.45 mmol/L], and > 4.5 mg/dL [1.45 mmol/L] by study visit are presented in Table 17. Normal range for serum phosphorus in adults is 2.5-4.5 mg/dL [0.81-1.45 mmol/L].

Table 15: Proportion of Subject Treated with KRN23 with Serum Phosphorus Levels by Categories (Efficacy Analysis Population) KRN23-INT-001

	Number (%) of Subject Treated with KRN23, N=27			
	Categories of Serum Phosphorus Levels (mg/dL)			
Visit Day /Relative Day	≤ 2 .5	> 2.5 to ≤ 3.5	> 3.5 to ≤ 4.5	> 4.5
Dosing Interval 1				
Visit 2 (Day 0)/0	26 (96.3)	1 (3.7)	0	0
Visit 4 (Day 7)/7	23 (85.2)	4 (14.8)	0	0
Visit 7 (Day 26)/26	26 (96.3)	1 (3.7)	0	0
Dosing Interval 2				
Visit 8 (Day 28)/0	26 (96.3)	1 (3.7)	0	0
Visit 10 (Day 35)/7	17 (63.0)	10 (37.0)	0	0
Visit 13 (Day 54)/26	25 (92.6)	2 (7.4)	0	0
Dosing Interval 3				
Visit 14 (Day 56)/0	23 (85.2)	2 (7.4)	0	0
Visit 16 (Day 63)/7	7 (25.9)	20 (74.1)	0	0
Visit 19 (Day 82)/26	19 (70.4)	8 (29.6)	0	0
Dosing Interval 4				
Visit 20 (Day 0)/0	18 (66.7)	6 (22.2)	0	0
Visit 22 (Day 91)/7	3 (11.1)	19 (70.4)	4 (14.8)	0
Visit 25 (Day 110)/26	14 (51.9)	12 (44.4)	0	0

Pharmacodynamic endpoints

The results from the pharmacodynamic endpoints Mean serum phosphorus, renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) and Mean serum 1,25(OH)2D are shown in Figure 13 for both studies KRN23-INT-001 and KRN23-INT-002

Serum markers of bone formation (bone-specific alkaline phosphatase [BALP], procollagen type 1 N-Terminal Propeptide [P1NP] and osteocalcin) and bone resorption (CTx and CTx/creatinine) tended to increase after burosumab dosing.

Patient Reported Outcomes (PRO)

Two PRO instruments (SF-36v2 and WOMAC) were used in the study.

KRN23-INT-002

Study Title

An Open-Label, Long-Term, Extension Study to Evaluate the Safety and Efficacy of KRN23 in Adult Subjects with X-Linked Hypophosphatemia

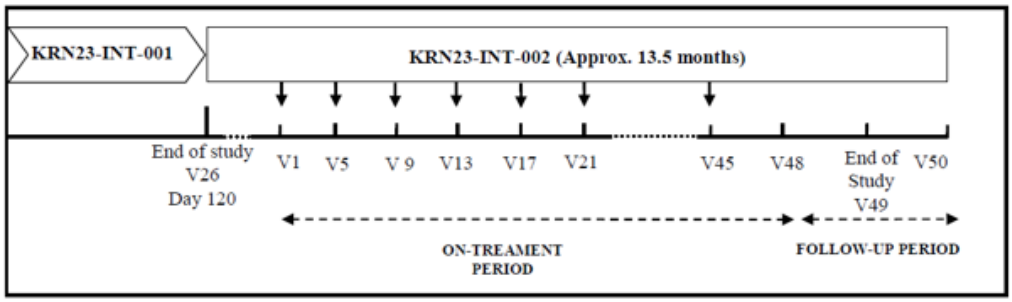
Study Design

This was a Phase 1/2, open-label, repeat-dose, multicentre, long-term extension study in adults with a clinical diagnosis of XLH who satisfactorily completed Study KRN23-INT-001.

The study was designed to further assess the safety and efficacy of repeat-dose burosumab SC administration and its effects on PD, PK, immunogenicity, and HRQoL in these subjects.

The study consisted of 2 periods: On-treatment and Follow-up. At baseline of the On-treatment period, subjects were evaluated for eligibility to participate in this extension study. Eligible subjects were allowed to continue treatment with burosumab in the open-label portion of this extension study (Figure 12).

Figure 11: Study design KRN23-INT-002



The initial burosumab dose in this extension study was administered at the baseline visit (Visit 1) and was the same burosumab dose that the subject received on Day 84 in Study KRN23-INT-001, unless the subject's serum phosphorus level was >3.5 mg/dL [1.13 mmol/L] on Day 110 in Study KRN23-INT-001 or the peak serum phosphorus level was ≥4.2 mg/dL [1.36 mmol/L]. In such case, the subject's initial burosumab dose in the current study was reduced one dose level.

Subject Disposition and Baseline Characteristics

Please refer to Table 16.

Two subjects, both treated with KRN23, were discontinued from the study KRN23-INT-002 due to TEAEs (nephrolithiasis and nephrocalcinosis and restless legs syndrome). This is further discussed in the Safety section.

Exposure

A total of 22 subjects were treated with burosumab (21 in the open-label portion of the study and 1 in the bone substudy) and 1 subject was treated with placebo in the bone substudy. In this study, subjects received up to 12 SC doses of KRN23 at 0.05, 0.1, 0.3, 0.6, or 1.0 mg/kg once every 28 days.

Burosumab was administered to each subject in the range from 0.30 to 1.00 mg/kg in all dosing intervals except for Dose Interval 10, when the range was 0.10 to 1.00 mg/kg.
In the initial dosing interval in the study (Dose Interval 1), the mean ± SD burosumab dose was 0.54 ± 0.20 mg/kg, and the median was 0.60 mg/kg. In subsequent dosing intervals, mean burosumab dose was increased and varied in a narrow range (0.73 ± 0.28 mg/kg to 0.88 ± 0.22 mg/kg).

Results

Efficacy endpoint - Serum Phosphorus Levels

The primary efficacy endpoint in KRN23-INT-002 was the number and percentage of subjects with post-dose serum phosphorus levels ≤2.5 mg/dL [0.81 mmol/L], >2.5 to ≤3.5 mg/dL [0.81-1.13 mmol/L], >3.5 to ≤4.5 mg/dL [1.13-1.45 mmol/L], and >4.5 mg/dL [1.45 mmol/L].

At Baseline, all subjects had serum phosphorus levels <2.5 mg/dL [0.81 mmol/L]. 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 burosumab. The minimum and maximum reported number of subjects (%) in each serum phosphorus category for each relative day in dosing intervals 2-12 compared to the first dosing interval is summarised in Table 18.

Table 16: Proportion of subjects in each serum phosphorus category on Day 0, 7 and 14 of the first and subsequent dosing intervals in KRN23-INT-002 (summarised from CSR by Assessor)

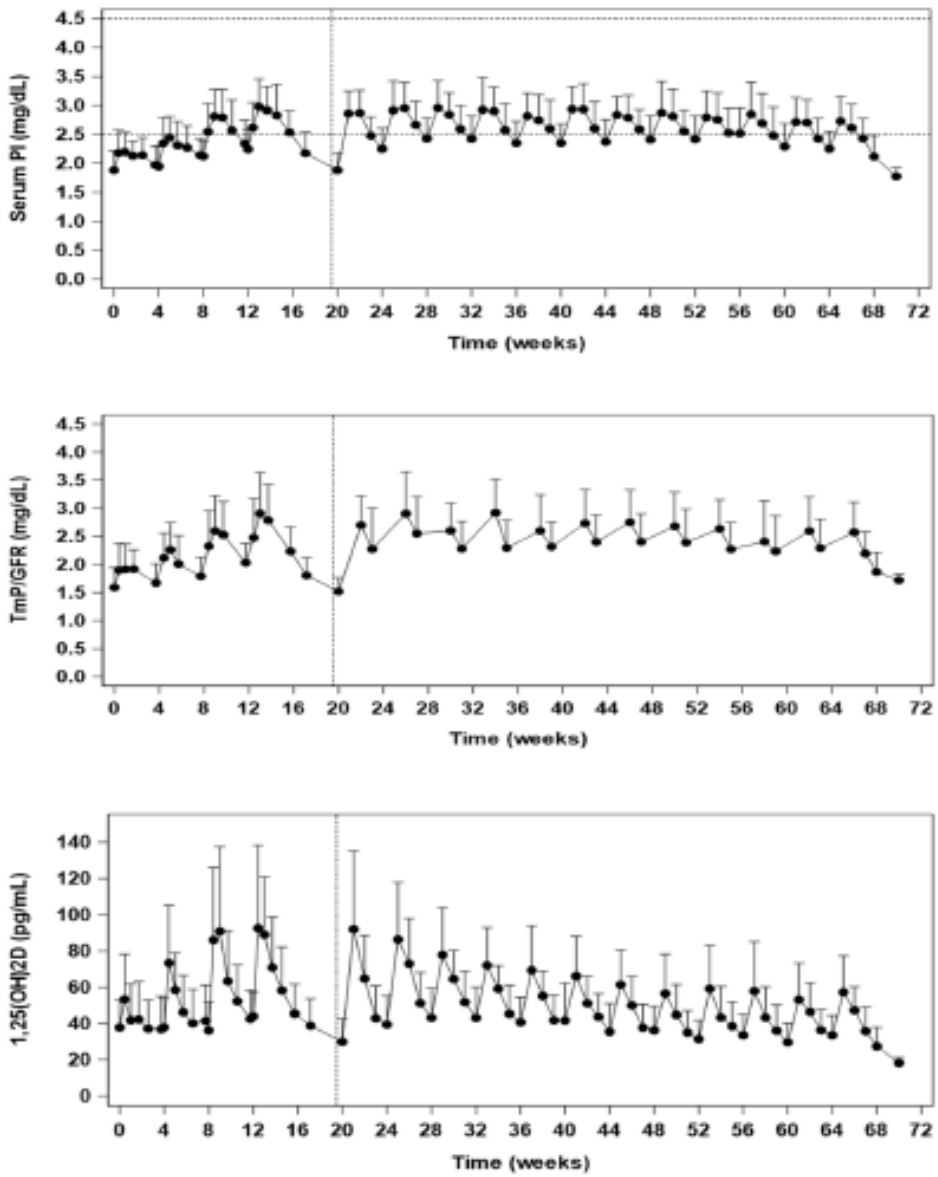
	Number (%) of Subjects Treated with KRN23 Serum Phosphorus Levels (mg/dL)			
Relative visit day	≤2.5	>2.5 to ≤3.5	>3.5 to ≤4.5	>4.5
First dosing interval				
Day 0	21 (100)	0 (0)	0 (0)	0 (0)
Day 7	4 (18)	17 (77)	0 (0)	0 (0)
Day 14	4 (18)	18 (82)	0 (0)	0 (0)
Subsequent dosing intervals (dosing interval 2-12)				
Day 0	Min 12 (57) Max 15 (75)	Min 5 (25) Max 9 (43)	Min 0(0) Max 3 (17)	0 (0)
Day 7	Min 3 (15) Max 8 (42)	Min 8 (44) Max 16 (80)	Min 0 (0) Max 3 (17)	0 (0)
Day 14	Min 3 (14) Max 9 (47)	Min 9 (47) Max 17 (81)	Min 0 (0) Max 2 (10)	0 (0)

The number of subjects at each visit was 17-22.

Pharmacodynamic endpoints

Changes in key pharmacodynamic parameters combined for KRN23-INT-001 and KRN23-INT-002 are shown in Figure 13. The final dose of burosumab was administered at Week 64.

Figure 12: Changes in Serum Phosphorus, TmP/GFR, and Serum 1,25(OH)2D Over Time in Studies KRN23-INT-001 and KRN23-INT-002



1,25(OH)2D = 1,25-dihydroxy vitamin D; PI = phosphorus (inorganic); TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; SD = standard deviation. Plotted values are mean (SD); Dotted horizontal line indicates the normal reference range for serum phosphorus. Dotted vertical lines indicate the transition from Study KRN23-INT-001 (n = 24-27) to KRN23-INT-002 (n = 18-22)

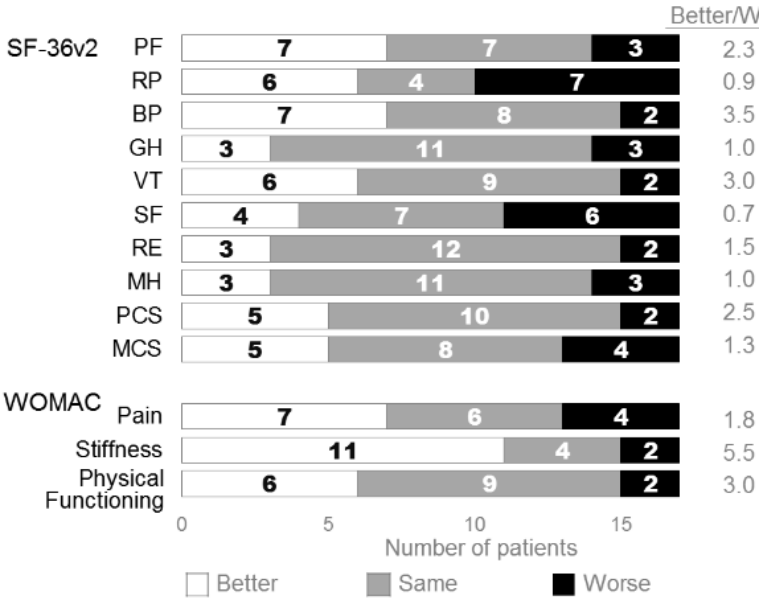
Peak and trough fluctuations of mean serum phosphorus were low throughout the study. The difference between mean peak and trough serum phosphorus levels for 12 available peak-trough pairs ranged from 10%-21%. Inter-subject variability for peak and trough fluctuations of serum phosphorus levels were also low (11%-19% for 12 available peak-trough pairs).

Patient-Reported Outcomes

The Minimally Important Change (MIC) is the smallest change over time in an individual patient's score that represents a clinically relevant change in their health status. Using a distributional approach with a US general population sample, MICs have been established for the SF-36v2 as: PF, 3.5 points; Role-Physical, 3.2; Bodily Pain, 4.5; General Health, 5.7; Vitality, 5.5; Social Functioning, 5.0; Role-Emotional, 3.8; Mental Health, 5.5; PCS, 3.1; and MCS, 3.8. The User's Manual for the WOMAC lists MICs as 9.7 for Pain, 10.0 for Stiffness, and 9.3 for Physical Functioning.

Figure 14 displays the number of patients who were classified as "better," "same," or "worse" according to the established MIC for each scale from baseline in KRN23-INT-001 to endpoint report in the KRN23-INT-002 completer population.

Figure 13: Number of Patients Better, Same or Worse by Endpoint (n=17)

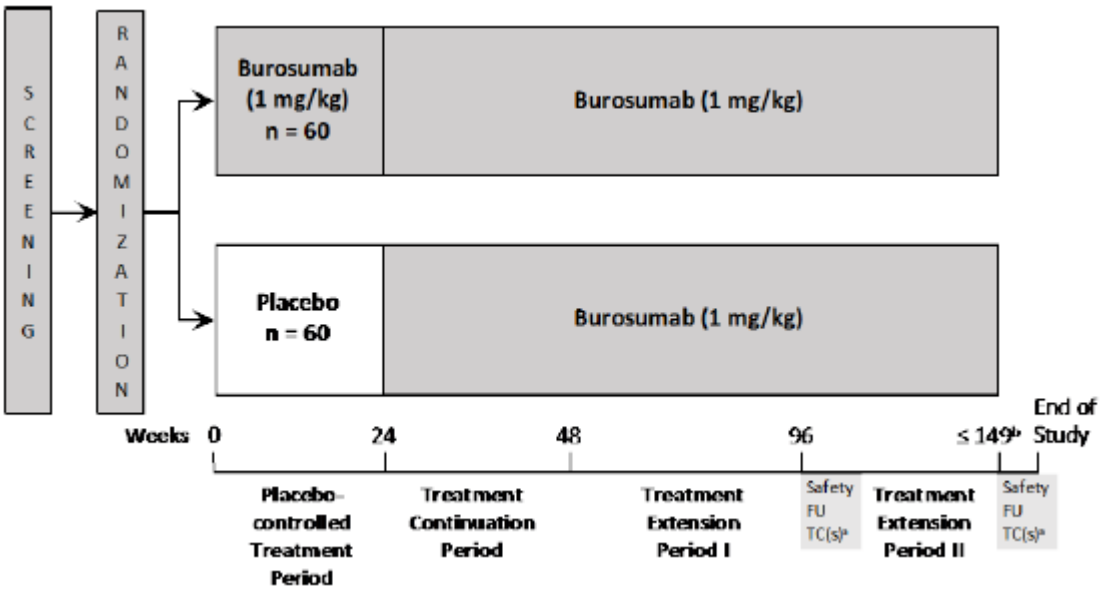


2.4.2. Main study

Study UX023-CL303

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study with Open-Label Extension to Assess the Efficacy and Safety of KRN23 in Adults with X-linked Hypophosphatemia (XLH)

Figure 14: UX023-CL303 Study Design Schema



The study comprises two Screening Visits, a Baseline Visit, a Placebo-controlled Treatment Period (24 weeks), an open-label Treatment Continuation Period (24 weeks), an open-label Treatment Extension Period I (48 weeks), and an open-label Treatment Extension Period II (US only; up to 53 weeks).

As of the data cut-off date for the report presented with the application, the study is ongoing, with all subjects having completed the Placebo-controlled Treatment Period (Week 24 Visit) and the Treatment Continuation Period (Week 48 visit) and now receiving open-label burosumab in the Treatment Extension Periods or having discontinued the study.

Methods

Study participants

Key inclusion criteria:

1. Male or female, aged 18-65 years
2. Diagnosis of XLH supported by classic clinical features of adult XLH (such as short stature or bowed legs) and at least ONE of the following at screening:
    - 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
3. Biochemical findings consistent with XLH at SV2 following overnight fasting (min. 8 hours):
    - Serum phosphorus < 2.5 mg/dL (0.81 mmol/L)
    - Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR) of < 2.5 mg/dL
4. Presence of skeletal pain attributed to XLH/osteomalacia, as defined by a score of ≥ 4 on BPI Worst Pain

5. Estimated glomerular filtration rate (eGFR) ≥60 mL/min (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation); OR eGFR of 45 to < 60 mL/min at SV2 with confirmation that the renal insufficiency was not due to nephrocalcinosis

Key exclusion criteria:

1. Use of a pharmacologic vitamin D metabolite or analogue (calcitriol, doxercalciferol, and paricalcitol) within 14 days prior to SV2
2. Use of oral phosphate within 14 days prior to SV2
3. Use of aluminium hydroxide antacids, acetazolamides, and thiazides within 7 days prior to SV2
4. Chronic use of systemic corticosteroids defined as more than 10 days in the 2 months prior to SV1
5. Corrected serum calcium level ≥10.8 mg/dL (2.7 mmol/L) at SV2
6. Serum intact parathyroid hormone (iPTH) ≥ 2.5 x ULN at SV1
7. Use of medication to suppress parathyroid hormone (PTH; cinacalcet for example) within 60 days prior to SV1
8. Use of bisphosphonates in the 2 years prior to SV1
9. Use of denosumab in the 6 months prior to SV1
10. Use of teriparatide in the 2 months prior to SV1

Treatments

During the Placebo-controlled Treatment Period, subjects randomized to burosumab was to receive 1.0 mg/kg of burosumab administered via SC injection Q4W (28 days), and subjects randomized to placebo received placebo administered via SC injection Q4W.

During the Treatment Continuation Period and Treatment Extension Period, all subjects was to receive 1.0 mg/kg of burosumab administered via SC injection Q4W.

The MAH presents the following arguments for using placebo as control instead of conventional therapy: A double-blind, active-comparator design would be very difficult given the differences in the method of administration (oral vs SC injection for burosumab) and individualized dosing (Linglart et al. 2014), (Carpenter 2012). Furthermore, because there is no consensus regarding its use in adults, treatment with oral phosphate and active vitamin D typically stops in adolescence; however, many adults experience long-term complications from the treatment, such as hyperparathyroidism and nephrocalcinosis. The benefit-risk profile of oral phosphate and vitamin D therapy has not been demonstrated in large randomized, controlled studies; therefore, a comparison of burosumab treatment versus placebo over a 24-week period was deemed appropriate and fundamental to demonstrate the benefit-risk profile of burosumab.

Objectives

The primary objective of this study is to establish the effect of burosumab treatment compared with placebo on increasing serum phosphorus levels in adults with XLH.

The key secondary efficacy objectives of the study are to establish the effect of burosumab treatment compared with placebo on skeletal pain, stiffness, and physical functioning.

Outcomes/endpoints

Primary Efficacy Endpoint

- The proportion of subjects achieving mean serum phosphorus levels above the lower level of normal (LLN) (2.5 mg/dL [0.81 mmol/L]) at the midpoint of the dose interval (ie, Weeks 2, 6, 10, 14, 18, and 22), as averaged across dose cycles between Baseline and Week 24.

Key Secondary Efficacy Endpoints

- Change from Baseline to Week 24 in BPI Worst Pain score
- Change from Baseline to Week 24 in the WOMAC Stiffness score
- Change from Baseline to Week 24 in the WOMAC Physical Function score

Additional Secondary Efficacy Endpoints

- Additional measures to assess serum phosphorus levels between Baseline and Week 24 included:
    - Proportion of subjects achieving mean serum phosphorus levels above the LLN at the end of the dose cycle (4 weeks after dosing), as averaged across dose cycles
    - Mean change from Baseline and percentage change from Baseline at the midpoint of each dose cycle, as averaged across dose cycles
    - Mean change from Baseline and percentage change from Baseline at the end of each dose cycle, as averaged across dose cycles
    - Time-adjusted AUC
- Change and percentage change from Baseline to post-Baseline visits in serum phosphorus, serum 1,25(OH)2D, urinary phosphorus, TmP/GFR, and TRP
- Change and percentage change from Baseline to post-Baseline visits in biochemical markers of bone remodelling, including P1NP, CTx, and BALP
- Change from Baseline to post-Baseline visits in BPI Worst Pain score
- Change from Baseline to post-Baseline visits in BPI Pain Severity score
- Change from Baseline to post-Baseline visits in BPI Pain Interference score
- Change from Baseline to post-Baseline visits in BFI Worst Fatigue score
- Change from Baseline to post-Baseline visits in BFI Global Fatigue Score
- Change from Baseline to post-Baseline visits in the WOMAC Stiffness score
- Change from Baseline to post-Baseline visits in the WOMAC Physical Function score

Exploratory efficacy objectives

- The number of active pseudofractures and/or fractures as defined by skeletal survey at baseline and the numbers and percentages of the baseline active pseudofractures/fractures that were healed, partially healed, unchanged, and worsened at post-baseline visits
- The number of subjects with baseline active pseudofractures and/or fractures and the numbers of those subjects who had changes from baseline to healed, partially healed, unchanged, and worsened at post-baseline visits

- Change from baseline to post-baseline visits in total calcaneal enthesopathy burden (sum of dimensions of superior and inferior calcaneal spurs bilaterally measured in two dimensions) measured by lateral foot X-rays
- Change from baseline to post-baseline visits in the PGI-I
- Change from baseline to post-baseline visits in the 6MWT total distance walked (meters)
- Change from baseline to post-baseline visits in the 6MWT percent predicted distance walked based on published normative data
- Change from Week 24 to visits after Week 24 in the TUG test completion time

Sample size

Determination of the sample size for this study was based on the assumption that the percentage of subjects who achieved mean serum phosphorus levels in the normal range at the midpoint of the dose interval from Baseline to Week 24 would be 60% and 10% in the burosumab and placebo groups, respectively. A sample size of 60 per group (total sample size of 120) provided > 95% power to detect a 50% difference between the burosumab and placebo treatment groups in the percentages of subjects achieving mean serum phosphorus levels at the midpoint and end of the dose intervals between Baseline and Week 24 at the two-sided level of significance of 0.05.

With a total sample size of 120 subjects, this study design also had ≥ 80% power to detect a mean difference of 1.0 in change from Baseline between the burosumab and placebo groups in BPI Worst Pain, assuming a mean change from Baseline of 2.0 in the burosumab group and 1.0 in the placebo group, a common standard deviation (SD) of 1.8, and a 10% drop-out rate.

Randomisation

Eligible subjects enrolled in the study were sequentially assigned an identification number. A randomisation schedule was developed by an independent party to maintain blinding. Subjects were randomised via an Interactive Web Randomization System (IWRS) and assigned in a 1:1 ratio to the burosumab or placebo treatment groups. Randomisation was stratified by pain intensity based on the patient diary score for the 7 days prior to the Baseline Visit (> 6.0 or ≤ 6.0). At least 4 of 7 diary days were required to derive the stratification for randomisation. Subjects with fewer than 4 completed diary days did not meet the eligibility requirement and were not to be randomised.

Note that per protocol, stratification by pain intensity was to be based on mean BPI Worst Pain; however, due to an error in the IWRS, BPI Average Pain was used instead. This was discovered during the course of study conduct. Given that study enrolment and dosing were already ongoing at the time that the IWRS error was identified, it was determined that the study should continue enrolment under the implemented stratification factor (BPI-Q5 Average Pain) instead of changing and correcting the BPI stratification factor back to the protocol specified BPI-Q3 Worst Pain midway into the study. The IWRS error was recorded as a protocol deviation in the electronic data capture (EDC) system.

In addition, sensitivity analyses for the primary and key secondary endpoints were implemented to assess the impact of this discrepancy of the stratification factors based on BPI Worst Pain and Average Pain.

Randomisation also was stratified by region (North America/EU, Japan, South Korea). Note that stratification by region was not specified in the protocol but was conducted for operational and logistic considerations to ensure balance between the 2 treatment groups, as small numbers of subjects were expected to be enrolled in Japan and South Korea.

No more than 70% female subjects were to be enrolled.

Blinding (masking)

The study was to be conducted under double-blind conditions through Week 24 implying that neither the Sponsor, subject, nor site personnel involved in study conduct would know the identity of a subject's treatment. Procedures implemented to achieve and maintain the double-blind status of the study included but was not limited to:

- Matched appearance of burosumab and placebo
- Central laboratory used for all post-baseline serum and urine parameters; site and Sponsor personnel were blinded to key laboratory values associated with expected changes from burosumab treatment during the Placebo-controlled Treatment Period
- Radiographs, ECHOs, renal ultrasounds, and ECGs were centrally read by individuals blinded to treatment assignment and subject data

Treatment assignment for an individual subject were to be unblinded by the Investigator only in an emergency, e.g., event concerning subject safety, and only if knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject.

If serum phosphorus increased above 5.0 mg/dL [1.61 mmol/L] at any time or increased above the ULN (4.5 mg/dL [1.45 mmol/L]) on two occasions, the subject treatment assignment was to be unblinded (during the Placebo-Controlled Treatment Period) and the actual dose was to be decreased by half. The Investigator were then to contact the medical monitor to determine when and how to further dose titrate. If unblinding was required for these serum phosphorus criteria, it was to be performed by the Medical Monitor via the "Peek Blind" function in IWRS.

The primary analysis of the study occurred after all subjects completed their Week 24 Visit. Selected sponsor personnel were unblinded to treatment assignments to conduct this analysis.

After their Week 24 Visit, all subjects received burosumab treatment. Subjects and investigators remained blinded to original double-blind treatment assignments until the Week 48 analysis was completed.

After the Interim Database Lock on 23 March 2017, the database was unlocked and relocked twice, in September 2017 and in October 2017, after meetings of the Database Unlock Impact Assessment Team. Each unlock and relock followed the internal appropriate SOP, which describes the procedures for any requests for data change after an Interim Database Lock. The data changes at the site level requiring the unlocks were: (1) WOMAC Stiffness; (2) six-minute walk test (6MWT) baseline distance (incorrect for one Subject due to a calculation error at the site); and (3) several AEs that investigators had updated or added after the Interim Database Lock.

Statistical methods

The Week 24 primary analysis was conducted after all subjects either completed the Placebo-controlled Treatment Period (i.e. the Week 24 Visit) or discontinued the study during that period. The Week 48 analysis was conducted after all subjects had completed the Week 48 assessments or discontinued from the study during the Treatment Continuation/Extension Period to assess longer-term treatment efficacy and safety. The week 24 and week 48 analysis respectively were reported separately.

Analysis populations

The primary analysis set used for the analysis of efficacy endpoints included all randomised subjects who received at least one dose of IP. Subjects were analysed according to the randomised treatment group, regardless of the actual treatment received.

The safety analysis set consisted of all randomised subjects who received at least one dose of IP and was used for the analyses of all safety endpoints. Subjects were analysed based on the actual treatment received.

The Treatment Continuation Analysis Set is the subset of randomised subjects that continued after the 24-week placebo-controlled treatment period and received at least one dose of study drug during the treatment continuation period. The Treatment Continuation Analysis set was used for the analysis of the efficacy and safety endpoints at week 48 analysis in addition to the primary analysis set and safety analysis set.

The Treatment Extension Analysis Set is the subset of randomised subjects that continued after the open-label Treatment Continuation Period and received at least one dose of study drug during the treatment extension period. The Treatment Extension Analysis set will be used for the analysis of the efficacy and safety endpoints at the Week 96 analysis in addition to the primary analysis set and safety analysis set.

Primary Efficacy Endpoint

The primary endpoint was analysed using a 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 factor used for randomisation (BPI Average Pain). In the case where no serum phosphorus data were available for 2 weeks post-dose between Baseline and Week 24, the subject was treated as a non-responder, defined as not achieving a serum phosphorus level above the LLN.

Key PROs Endpoints

The three key secondary efficacy endpoints were analysed using a generalized estimation equation (GEE) repeated measures analysis. The GEE model included treatment, actual randomisation stratification factor based on BPI Average Pain (> 6.0 or ≤ 6.0) if applicable, visit and interaction of treatment-by-visit as fixed factors with adjustment for baseline measurement. The stratification factor was not to be included in the GEE model for the change from baseline in BPI Worst Pain as the baseline BPI Worst Pain is highly correlated to the randomisation stratification factor based on BPI Average Pain. The covariance structure that was to be used was a compound symmetry which specifies constant variance for the assessments and constant covariance between the assessments over time. In general, the p-value for testing the statistical significance of the change from the baseline to week 24 (Placebo-Controlled Treatment Period) between the two treatment groups was to be provided. Type III tests for the LS means were to be used for the statistical comparison; the 95% CI will also be reported.

The following sensitivity analyses were planned:

•For BPI Worst Pain, WOMAC Stiffness and Physical Function): analyses based on the GEE model repeated using mBOCF, LOCF and BOCF imputation methods.

Handling of Missing and Incomplete Data

If no serum data was available to evaluate the primary endpoint, non-responder imputation was used, and hence, the subject was considered as not achieving a serum phosphorus level above the LLN.

In the analyses of change from baseline (for example, BPI, WOMAC), only subjects with a baseline and at least one post-baseline measurement was included in the analysis.

The following imputation rules were to be applied to derive the BPI and BFI endpoints at each visit.

1.If the score for the endpoint was missing at the scheduled visit, the endpoint was to be set to missing at this visit.
2. Otherwise, for the endpoints of BPI pain severity dimensions, BPI severity score and BFI fatigue severity items 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 to be used for this visit.
3. Otherwise, the average of the non-missing diary scores and the score recorded at the visit was to be used for this visit.

For computing the domain scores at each visit for each subject, the WOMAC missing data algorithm was as follows:
1. If two or more Pain items, both Stiffness items, or four or more Physical Functioning items are missing, then the corresponding scale score is set to missing.
2. Otherwise, any missing item is replaced with the mean of the other items in its scale, and scales are then calculated normally.

Sensitivity analyses for the key secondary endpoints were performed using LOCF (Last Observation Carried Forward), BOCF (Baseline Observation Carried Forward) and mBOCF (modified Baseline Observation Carried Forward) imputation method. The imputation for the mBOCF analysis was defined as follows:

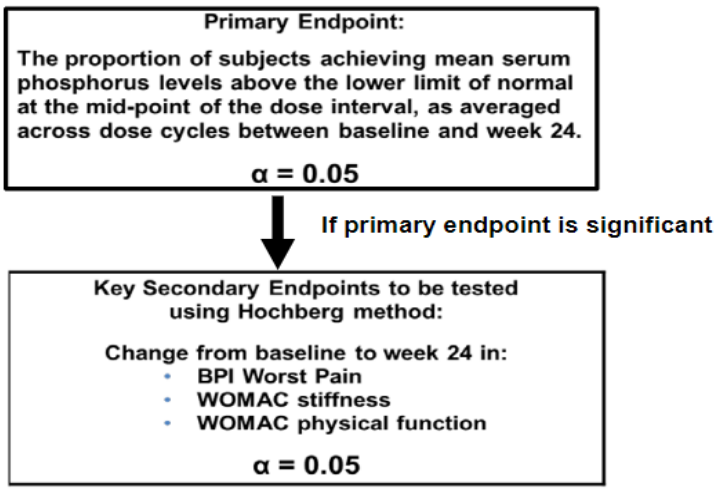
•For discontinuations due to AE or death, use the worst between BOCF (Baseline Observation Carried Forward) and LOCF (Last Observation Carried Forward)
•Otherwise use LOCF.

Multiple Comparisons/Multiplicity
In order to control the family-wise error rate (FWER) at the 0.05 level, the following method was used for multiple testing with regards to the primary and the key secondary efficacy endpoints of PROs for the week 24 primary analysis.

•Step 1: Testing 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, as averaged across dose cycles between baseline and week 24. If the burosumab treatment group is superior to the placebo group (p-value < 0.05 by a two-sided test), then go to Step 2, otherwise stop testing.

•Step 2: Testing the three key secondary endpoints of PROs (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. The Hochberg adjustment were applied for multiple testing for the three endpoints.

Flow Chart of Multiplicity Adjustment



Hochberg Method

	p-value	Signif.	p-value	Signif.	p-value	Signif.	p-value	Signif.
Key Secondary Endpoint (1)	≤0.05	Y	>0.05	N	>0.05	N	>0.05	N
Key Secondary Endpoint (2)		Y	≤0.025	Y	>0.025	N	>0.025	N
Key Secondary Endpoint (3)		Y		Y	≤0.0167	Y	>0.0167	N

Key Secondary endpoints were ranked by p-values from highest to lowest (1 to 3).

Sensitivity analyses due to randomisation error

Sensitivity analyses for the primary and key secondary endpoints were implemented to assess the impact of this discrepancy of the stratification factors based on BPI Worst Pain and Average Pain (see above). To assess the relationship of the stratification variables based on BPI Worst Pain and BPI Average Pain, the Pearson Correlation Coefficient was obtained on the continuous variables of BPI Worst Pain and Average Pain. A contingency table between the categorical stratification factors (> 6.0 or ≤ 6.0) based on BPI Worst Pain and Average Pain has also been provided by total and treatment groups.

• A sensitivity analysis of the primary endpoint was performed using the protocol specified randomisation stratification factor based on BPI Worst Pain (> 6.0 or ≤ 6.0) to substitute for the actual randomisation stratification factor based on BPI Average Pain.

•For change from baseline to week 24 in BPI Worst Pain; an analysis adjusting for the baseline BPI Average Pain score instead of the baseline BPI Worst pain score in the GEE model.

•For change from baseline to week 24 in WOMAC Stiffness and Physical Function scales; analyses were performed using the planned stratification factor based on the BPI Worst Pain (> 6.0 or ≤ 6.0) instead of the actual stratification factor based on BPI Average Pain (> 6.0 or ≤ 6.0) in the GEE model.

Week 48 analyses (the Treatment Continuation Period)

Statistical analyses will be reported using summary tables, figures, and data listings. Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard deviation, median, quartiles, minimum, and maximum will be provided. For discrete data, frequency and percent distributions will be provided. For time-to-event data, Kaplan-Meier estimates will be provided. For longitudinal analysis of endpoints measured over time, GEE analysis will be used.

Results UX023-CL303

Participant flow

A total of 163 subjects were screened for this study, of whom 134 subjects were enrolled and randomized 1:1 to burosumab (68 subjects) or placebo (66 subjects). Subject disposition is shown in Table 19.

Table 17: Subject Disposition (All Randomized Subjects)

	Placebo (N = 66) n (%)	Burosumab (N = 68) n (%)	Total (N = 134) n (%)
Subjects Randomized	66 (100.0)	68 (100.0)	134 (100.0)
Primary Analysis Set	66 (100.0)	68 (100.0)	134 (100.0)
Safety Analysis Set	66 (100.0)	68 (100.0)	134 (100.0)
Pharmacokinetics Analysis Set	66 (100.0)	68 (100.0)	134 (100.0)
Treatment Continuation Analysis Set	66 (100.0)	67 (98.5)	133 (99.3)
Treatment Extension Analysis Set	63 (95.5)	63 (92.6)	126 (94.0)
Placebo-controlled Treatment Period			
Subjects Who Completed	66 (100.0)	67 (98.5)	133 (99.3)
Subjects Who Discontinued	0	1 (1.5)	1 (0.7)
Reason for Discontinuation			
Subject Withdrew Consent	0	1 (1.5)	1 (0.7)
Treatment Continuation Period			
Subjects who Completed	63 (95.5)	63 (92.6)	126 (94.0)
Subjects who Discontinued	3 (4.5)	4 (5.9)	7 (5.2)
Reasons for Discontinuation			
Subject Withdrew Consent	0	1 (1.5)	1 (0.7)
Other	3 (4.5)	3 (4.4)	6 (4.5)
Treatment Extension Period (Through Cutoff Date)			
Subjects Who Discontinued	1 (1.5)	0	1 (0.7)
Reason for Discontinuation	1 (1.5)	0	1 (0.7)
Other	1 (1.5)	0	1 (0.7)

The most common reason for screen failure (reported for 10 subjects) was failure to meet the inclusion criterion requiring presence of skeletal pain attributed to XLH/osteomalacia, as defined by a score of ≥ 4 on BPI Worst Pain at SV1. The next most common reason (5 subjects) was meeting the exclusion criterion of having serum iPTH ≥ 2.5 x ULN at SV1.

All but one subject, who was in the burosumab group, completed the 24-week Placebo-controlled Treatment Period. The subject who discontinued withdrew consent for participation in the study after approximately 6 months of treatment (last dose of burosumab administered approximately 1 month before study withdrawal) and did not complete the Week 24 Visit assessments.

Per the protocol, the planned randomisation stratification was BPI pain intensity based on the mean of the 7 days of BPI Worst Pain diary scores prior to baseline visit. Due to an error in the IWR, the actual randomisation stratification was based on the mean of the BPI Average Pain scores prior to baseline.

As shown in Table 20, for approximately 60% of subjects, their actual BPI Average Pain randomisation stratification category and their planned BPI Worst Pain randomisation stratification categories were the same (e.g., if their planned stratification category was ≤6.0, their actual stratification category also was ≤ 6.0).

The Pearson correlation coefficient between these categories was 0.82256 ($p < 0.0001$), showing that these categories were highly associated and indicating that with regard to randomisation of individual subjects, the impact of the stratification misclassification was likely minimal.

Table 18: Randomization Stratification Categories (Primary Analysis Set) UX023-CL303

	Placebo (N = 66) n (%)	Burosumab (N = 68) n (%)	Total (N = 134) n (%)
Actual Pain Intensity Randomization Stratification Based on BPI Average Pain[a]			
≤ 6.0	49 (74.2)	48 (70.6)	97 (72.4)
> 6.0	17 (25.8)	20 (29.4)	37 (27.6)
Planned Pain Intensity Randomization Stratification Based on BPI Worst Pain[a]			
≤ 6.0	27 (40.9)	17 (25.0)	44 (32.8)
> 6.0	39 (59.1)	51 (75.0)	90 (67.2)
Actual & Planned Randomization Stratification[a]			
≤ 6.0 & ≤ 6.0	26 (39.4)	17 (25.0)	43 (32.1)
≤ 6.0 & > 6.0	23 (34.8)	31 (45.6)	54 (40.3)
> 6.0 & ≤ 6.0	1 (1.5)	0	1 (0.7)
> 6.0 & > 6.0	16 (24.2)	20 (29.4)	36 (26.9)
Region			
North America/EU	58 (87.9)	58 (85.3)	116 (86.6)
Japan	5 (7.6)	6 (8.8)	11 (8.2)
South Korea	3 (4.5)	4 (5.9)	7 (5.2)

a Per the protocol, the planned randomization stratification was BPI pain intensity based on the mean of the 7 days of BPI Worst Pain diary scores prior to baseline visit. The actual randomization stratification was based on the mean of the BPI Average Pain scores prior to baseline. The baseline BPI Worst Pain and BPI Average Pain are defined as the mean of the BPI Worst Pain and BPI Average Pain for 8 days including the 7 days of diary scores prior to baseline visit and the baseline visit score, respectively.

Recruitment

This study is being conducted at 25 study centres, including 8 in the US, 5 each in the United Kingdom and Japan, 3 in France, 2 in South Korea, and 1 each in Ireland and Italy.

The study started October 22, 2015 (Date first subject signed informed consent). Data cut-off date for the current application was June 08, 2017.

Conduct of the study

Protocol amendments

Protocol UX023-CL303 (dated 05 June 2015) was modified by three amendments:

Amendment 1 (dated 21 July 2016)

The main purpose of Amendment 1 was to incorporate feedback from regulatory authorities, modify or clarify certain procedures, correct inconsistencies, and remove redundant wording.

Key elements:

- A 48-week Extension Period was added to the study design.
- Enthesopathy was added as an efficacy measure in the study. The TUG test was added as an exploratory endpoint.

- A provision was added to allow additional testing for mutations consistent with syndromes with overlapping clinical and biochemical characteristics as XLH if the initial PHEX mutation analysis was negative or inconclusive and informed consent was provided by the subject.

Amendment 2 (dated 08 September 2016)

The main purpose of Amendment 2 was to clarify language and procedures and correct inconsistencies.

Amendment 3 (dated 31 Mar 2017)

The main purpose of Amendment 3 was to modify the categorization of the secondary efficacy objectives of the study (i.e., as "key" and "other") and corresponding secondary endpoints, to update the exploratory endpoints, and to update the planned statistical analyses. In addition, randomisation stratification was clarified, contraception requirements were updated, Safety Follow-up telephone calls (TCs) were added, the treatment duration was extended for study sites in the United States (US), subject or caregiver administration of study drug in the home setting in the US was added, and the Coordinating Investigator designated for this study was added. Minor edits and typographical corrections have also been made.

Key elements:

- Change from baseline to Week 24 in the WOMAC Stiffness score and Change from baseline to Week 24 in the WOMAC Physical Function score were identified as key secondary efficacy endpoints in addition to Change from baseline to Week 24 in BPI-Q3 (Worst Pain) score.
- Randomization stratification was updated to clarify that randomization was stratified not only by baseline pain intensity, but also by region (North America/European Union, Japan, and South Korea).
- A second Treatment Extension Period that included up to approximately 53 additional weeks of burosumab treatment was added for subjects enrolled at sites in the US only. In addition, Safety Follow-up telephone calls (TCs) over an interval of up to 8 weeks following the End of Study or Early Termination Visit were added. The maximum study duration consequently was changed to up to approximately 157 weeks. For subjects outside of the US, the duration of study treatment remained 96 weeks, followed by Safety Follow-up TCs over an interval of up to 8 weeks.

Protocol deviations

As of the data cut-off date for this report, 71 subjects (41 burosumab, 30 placebo) had major protocol deviations (Table 21).

Table 19: Major Protocol Deviations (All Randomized Subjects)

Type of Deviation	Placebo (N = 66) n (%)	Burosumab (N = 68) n (%)	Total (N = 134) n (%)
Subjects with Any Major Protocol Deviation	30 (45.5)	41 (60.3)	71 (53.0)
Informed Consent	10 (15.2)	12 (17.6)	22 (16.4)
Investigational Product	2 (3.0)	2 (2.9)	4 (3.0)
Procedure Not Done	13 (19.7)	16 (23.5)	29 (21.6)
Study Inclusion or Exclusion Criteria	2 (3.0)	5 (7.4)	7 (5.2)
Receipt of Prohibited Concomitant Medications	0	2 (2.9)	2 (1.5)
Unblinding	0	2 (2.9)	2 (1.5)
Out of Window Visit/Assessment	2 (3.0)	1 (1.5)	3 (2.2)
Other	13 (19.7)	14 (20.6)	27 (20.1)

Most major deviations involved procedures not done (21.6%; e.g., required fasting before laboratory assessments was not of full duration or fasting status was not recorded, corrected calcium for eligibility

was verified at SV1 instead of SV2), other (20.1%; e.g., required fasting time was not recorded or fasting was not of full duration, ECHO performed by a cardiologist not declared on the delegation log), or informed consent (16.4%; e.g., re-consent not performed in a timely manner).

Exposure

In both treatment groups, the median weight-based dose of study drug was 1.0 mg/kg (mean: 0.99 mg/kg; range: 0.6 – 1.1) at the Baseline Visit and remained between 0.9 and 1.0 mg/kg (mean: 0.87-0.98 mg/kg; range: 0.2 – 1.2) at all post-Baseline visits.

The protocol included criteria for treatment assignment unblinding and dose adjustments due to elevated serum phosphorus levels over upper level of normal (ULN) (>4.5 mg/dL [1.45 mmol/L]). Most subjects did not require dose adjustments. During the Placebo-controlled Treatment Period, 5 (7.4%) subjects in the burosumab group and no subject in the placebo group had treatment unblinded per protocol. Across all treatment periods, the dose of burosumab was reduced to 0.5 mg/kg in 11 (8.2%) subjects and subsequently maintained at that dose in 10 of the 11 subjects.

Baseline data

Baseline demographics

Table 20: Demographics (Primary Analysis Set)

Parameter Statistics	Placebo (N = 66)	Burosumab (N = 68)	Total (N = 134)
Age (years)			
Mean	38.65	41.29	39.99
SD	12.756	11.582	12.201
Min, Max	18.5, 65.5	20.0, 63.4	18.5, 65.5
Age Group (years) – n (%)			
18 to 50	56 (84.8)	52 (76.5)	108 (80.6)
>50 to 65	10 (15.2)	16 (23.5)	26 (19.4)
Sex – n (%)			
Male	23 (34.8)	24 (35.3)	47 (35.1)
Female	43 (65.2)	44 (64.7)	87 (64.9)
Primary Race – n (%)			
Asian	9 (13.6)	12 (17.6)	21 (15.7)
Black or African American	3 (4.5)	0	3 (2.2)
White	53 (80.3)	55 (80.9)	108 (80.6)
Other	1 (1.5)	1 (1.5)	2 (1.5)
Ethnicity – n (%)			
Hispanic or Latino	5 (7.6)	7 (10.3)	12 (9.0)
Not Hispanic or Latino	61 (92.4)	61 (89.7)	122 (91.0)
Weight (kg)			
Mean	71.27	70.06	70.65
SD	18.892	19.004	18.887
Min, Max	36.1, 126.6	37.1, 139.6	36.1, 139.6
Height (cm) [a]			
Mean	152.69	152.15	152.42
SD	11.836	9.491	10.672
Min, Max	120.6, 175.0	126.2, 176.0	120.6, 176.0
Body Mass Index (kg/m^2) [a]			
Mean	30.60	29.98	30.28
SD	7.789	7.485	7.614
Min, Max	17.4, 58.6	19.7, 64.6	17.4, 64.6

a n = 65 placebo, 67 burosumab

XLH medical history.

Table 21: XLH Medical History (Safety Analysis Set)

Parameter Statistics	Placebo (N = 66)	Burosumab (N = 68)	Total (N = 134)
Time since first XLH symptoms (years)			
N	32	28	60
Mean	38.44	35.83	37.22
SD	13.168	12.392	12.771
Min, Max	17.8, 65.6	6.0, 57.9	6.0, 65.6
Time since XLH diagnosis (years)			
N	42	39	81
Mean	31.36	31.47	31.41
SD	15.791	15.592	15.597
Min, Max	0.5, 64.7	0.5, 55.8	0.5, 64.7
Has ever experienced osteoarthritis? – n (%)			
Yes	38 (57.6)	47 (69.1)	85 (63.4)
No	28 (42.4)	21 (30.9)	49 (36.6)
Has ever experienced any of these renal conditions? – n (%)			
Yes	12 (18.2)	19 (27.9)	31 (23.1)
Nephrocalcinosis (calcium deposits in kidneys)	5 (7.6)	11 (16.2)	16 (11.9)
Nephrolithiasis (kidney stones)	8 (12.1)	10 (14.7)	18 (13.4)
No	54 (81.8)	49 (72.1)	103 (76.9)
Has ever experienced any of these dental/oral conditions? – n (%)			
Yes	55 (83.3)	60 (88.2)	115 (85.8)
Dental implant surgery (to replace missing teeth)	12 (18.2)	9 (13.2)	21 (15.7)
Excessive cavities (caries)	32 (48.5)	42 (61.8)	74 (55.2)
Extractions of adult teeth	35 (53.0)	43 (63.2)	78 (58.2)
Root canal surgery	32 (48.5)	42 (61.8)	74 (55.2)
Tooth abscess	41 (62.1)	44 (64.7)	85 (63.4)
No	11 (16.7)	8 (11.8)	19 (14.2)
Has ever experienced any orthopedic surgeries? – n (%)			
Yes	47 (71.2)	45 (66.2)	92 (68.7)
No	19 (28.8)	23 (33.8)	42 (31.3)

Baseline serum phosphorus is summarised in Figure 16.

Figure 15: Baseline serum phosphorus (UX023-CL303)

Parameter Statistics	Placebo (N = 66)	Burosumab (N = 68)	Total (N = 134)
Serum Phosphorus (mg/dL[a]), n	66	68	134
Mean (SD)	1.92 (0.316)	2.03 (0.304)	1.98 (0.314)
Median (min, max)	1.90 (1.3, 2.6)	2.00 (1.3, 3.0)	2.00 (1.3, 3.0)

Prior conventional therapy

Table 22: Prior Conventional Therapy

Category Parameter Statistics	Placebo (N = 66)	Burosumab (N = 68)	Total (N = 134)
Phosphate/vitamin D metabolites or analogs ever – n (%)			
Phosphate only	1 (1.5)	3 (4.4)	4 (3.0)
Vitamin D metabolites or analogs only	3 (4.5)	3 (4.4)	6 (4.5)
Phosphate and vitamin D metabolites or analogs	62 (93.9)	59 (86.8)	121 (90.3)
No phosphate/vitamin D metabolites or analogs	0	3 (4.4)	3 (2.2)
Phosphate (years)			
n	63	62	125
Mean	16.2	16.8	16.5
SD	10.18	10.68	10.39
Min, Max	1, 45	1, 44	1, 45
Vitamin D metabolites or analogs only (years)			
n	65	62	127
Mean	17.5	19.0	18.2
SD	11.93	9.97	11.00
Min, Max	1, 52	2, 46	1, 52
Phosphate/vitamin D metabolites or analogs before the age of 18 years – n (%)			
Phosphate only	2 (3.0)	5 (7.4)	7 (5.2)
Vitamin D metabolites or analogs only	4 (6.1)	5 (7.4)	9 (6.7)
Phosphate and vitamin D metabolites or analogs	48 (72.7)	45 (66.2)	93 (69.4)
No phosphate/vitamin D metabolites or analogs	12 (18.2)	13 (19.1)	25 (18.7)
Phosphate (years)			
n	50	48	98
Mean	8.2	8.8	8.5
SD	9.72	8.52	9.11
Min, Max	1, 40	1, 33	1, 40
Vitamin D metabolites or analogs (years)			
n	56	53	109
Mean	9.1	9.5	9.3
SD	10.79	8.38	9.65
Min, Max	1, 47	1,33	1, 47

Prior medical history

Conditions noted most commonly in subjects' medical history (> 30% of subjects) were in the SOCs of surgical and medical procedures (56.7%); musculoskeletal and connective tissue disorders (40.3%); and nervous system disorders (31.3%). Events most commonly reported in subjects' medical history (> 15% of subjects) were hypertension (25.4%), osteotomy (17.9%), and seasonal allergy (15.7%).

The conditions were generally well balanced between the treatment arms. Musculoskeletal and connective tissue disorders were more common in subjects randomised to burosumab (44% vs 36%), as were General disorders and administration site conditions (mainly pain, fatigue and pyrexia) (21% vs 14%) and Ear and labyrinth disorders (21% vs 9%) whereas Vascular disorders (mainly hypertension) was more common in subjects randomised to placebo (32% vs 25%).

The baseline pain medication per the subjects' pain diaries is presented in Table 25.

Table 23: Baseline Pain Medication Use (Primary Analysis Set)

	Placebo (N = 66) n (%)	Burosumab (N = 68) n (%)	Total (N = 134) n (%)
Any Pain Medication Use at Baseline			
Yes	44 (66.7)	47 (69.1)	91 (67.9)
No	22 (33.3)	21 (30.9)	43 (32.1)
Pain Medication Use at Baseline by Category			
Opioids			
Yes	13 (19.7)	17 (25.0)	30 (22.4)
No	53 (80.3)	51 (75.0)	104 (77.6)
Non-Opioid Pain Medications[a]			
Yes	43 (65.2)	47 (69.1)	90 (67.2)
No	23 (34.8)	21 (30.9)	44 (32.8)
Neuropathic Pain Medications/Antidepressants			
Yes	3 (4.5)	4 (5.9)	7 (5.2)
No	63 (95.5)	64 (94.1)	127 (94.8)
Other Pain Medications			
Yes	1 (1.5)	7 (10.3)	8 (6.0)
No	65 (98.5)	61 (89.7)	126 (94.0)

a Non-opioid pain medication is defined as nonsteroidal anti-inflammatory drugs and acetaminophen/paracetamol.

Baseline Genetic Status

Table 24: Baseline PHEX Mutation (Primary Analysis Set)

Parameter Statistics	Placebo (N = 66) n (%)	Burosumab (N = 68) n (%)	Total (N = 134) n (%)
PHEX mutation result			
Pathogenic	50 (75.8)	45 (66.2)	95 (70.9)
Likely Pathogenic	7 (10.6)	8 (11.8)	15 (11.2)
Variant of Uncertain Significance	8 (12.1)	9 (13.2)	17 (12.7)
Likely Benign	0	0	0
No Mutation	1 (1.5)	6 (8.8)	7 (5.2)
Zygosity			
Heterozygous	42 (63.6)	41 (60.3)	83 (61.9)
Mosaic	1 (1.5)	0	1 (0.7)
Hemizygous	22 (33.3)	21 (30.9)	43 (32.1)
No Mutation	1 (1.5)	6 (8.8)	7 (5.2)

PHEX = Phosphate-regulating gene with Homologies to Endopeptidases on the X-chromosome

No PHEX mutation was identified for seven (5%) subjects, including six in the burosumab group and one in the placebo group. The seven subjects, for whom mutations in the PHEX gene were not identified, were clinically diagnosed with XLH and met the inclusion criterion for support of the diagnosis of XLH. Four of the subjects (all in the burosumab group) had directly related family members with an inheritance pattern consistent with X-linked disease.

Numbers analysed

All 134 randomized subjects (100.0%) received at least one dose of study drug in the Placebo-controlled Treatment Period and were included in the Primary and Safety Analysis Sets.

All 134 of the subjects in the Safety Analysis Set had at least one evaluable PK concentration and were included in the PK Analysis Set.

Outcomes and estimation

Model-based estimates for WOMAC Stiffness, 6MWT, and fractures were reanalysed for the Placebo-controlled Treatment Period because additional or corrected data were provided for these endpoints after the Interim Database Lock for the primary analysis. Efficacy analyses for the Week 24 CSR were used for other model-based estimates in the Placebo-controlled Treatment Period. The Week 48 analysis was used for all other efficacy data, including mean/SD at every visit, and LS mean (SE) at visits after Week 24.

Primary Endpoint

The primary endpoint of this study was the proportion of subjects achieving mean serum phosphorus levels above the lower level of normal (LLN; 2.5 mg/dL [0.81 mmol/L])) at the midpoint of the dose interval (i.e., 2 weeks after each dose of study drug, the time of peak PD effect), as averaged across dose cycles between Baseline and Week 24.

Table 25: Primary Endpoint - Primary Analysis (CMH Test Adjusting for Region and Actual Randomization Stratification Based on BPI Average Pain) (Primary Analysis Set)

Parameter Statistics	Placebo (N = 66)	Burosumab (N = 68)
Achieved Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24 - n (%)	5 (7.6)	64 (94.1)
95% CI[a]	(3.3, 16.5)	(85.8, 97.7)
p-value[b]		< 0.0001

The 95% CIs for the proportion of subjects who achieve mean serum phosphorus levels above the LLN are calculated using the Wilson score method.
The p-value is from Cochran-Mantel-Haenszel (CMH) testing for association between achieving mean serum phosphorus levels above the LLN and treatment group, adjusting for the actual randomization stratification of BPI Average Pain and region.

Primary Endpoint -- Sensitivity Analysis

A prespecified sensitivity analysis adjusting for region and for the planned randomization stratification based on BPI Worst Pain produced results similar to those of the primary analysis ($p < 0.0001$). This indicates that the randomization stratification misclassification had minimal impact on the results for the primary endpoint.

Primary Endpoint -- Subgroup Analyses

Prespecified subgroup analyses of the primary endpoint by baseline BPI Worst Pain (≤6.0, > 6.0), actual randomization stratification factor based on BPI Average Pain (≤6.0, > 6.0), and geographic region (North America/EU, Japan, South Korea) were performed using the Fisher's Exact test to compare between the treatment groups.

The baseline demographics were not fully balanced between the subgroups. The >6.0 subgroup had a greater percentage of females (67%) and also had a greater percentage of subjects from North America/EU (90%) than the ≤6.0 subgroup (55% and 79%, respectively). The >6.0 subgroup had a smaller percentage of Asian subjects (13%) than the ≤6.0 subgroup (24%). In addition, the >6.0 subgroup had a greater percentage of subjects who received conventional therapy with both phosphate and vitamin D metabolites or analogues after the age of 18 years (75%) than the ≤6.0 subgroup (63%).

Results of the analyses for the BPI Worst Pain and Average Pain subgroups were similar to those of the primary analysis for the overall population, demonstrating that in each of the subgroups, a statistically significantly greater percentage of subjects in the KRN23 group (ranging from 93% to 100% across the four subgroups) achieved a serum phosphorus concentration above the LLN across the midpoints of the dose intervals through Week 24 compared with the placebo group (ranging from 5% to 13% across the subgroups) ($p < 0.0001$).

In analyses of the subgroups based on region, results for the North America/EU and Japan subgroups were similar to those of the analysis of the overall population. In each of these subgroups, a statistically significantly greater percentage of subjects in the KRN23 group (97% in North America/EU, 100% in Japan) achieved a serum phosphorus concentration above the LLN across the midpoints of the dose intervals through Week 24 than in the placebo group (9% in North America/EU, 0% in Japan) ($p \leq 0.0022$).
For the subgroup of subjects from South Korea, which included only four subjects in the KRN23 group and three subjects in the placebo group, a significant difference between treatment groups was not observed. Two (50%) of the subjects in the KRN23 group achieved a serum phosphorus concentration above the LLN across the midpoints of the dose intervals through Week 24, compared with no subjects in the placebo group.

Results of additional subgroup analyses of the primary endpoint by sex and race (white, non-white) also were similar to those of the analysis for the overall population, demonstrating that in each of the subgroups, a notably greater percentage of subjects in the KRN23 group (ranging from 85% to 96% across the subgroups) achieved a serum phosphorus concentration above the LLN across the midpoints of the dose intervals through Week 24 than in the placebo group (ranging from 0% to 9% across the subgroups).

Seven subjects, six in the KRN23 group and one in the placebo group, did not have identified PHEX mutations at baseline but were clinically diagnosed with XLH and met the inclusion criterion for support of the diagnosis of XLH with FGF23 serum concentrations at baseline >30 pg/mL. All six of the subjects in the KRN23 group achieved a serum phosphorus concentration above the LLN across the midpoints of the dose intervals through Week 24; each also had a serum phosphorus concentration within the normal range at Week 24. Serum phosphorus levels in the subject in the placebo group remained below the LLN through Week 24.

Key secondary endpoints

Per the Hochberg multiplicity adjustment specified in the Statistical Analysis Plan, because the result of the primary endpoint primary analysis was statistically significant, the key 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 at the 0.05 significance level. The three endpoints were analysed using generalised estimation equation repeated measure analysis and tested as a group with Hochberg multiplicity adjustment, in which the nominal p-values for the endpoints were ordered from the largest to the smallest to determine the significance level at which they were tested (Table 28).

Data is presented graphically in Figure 17, Figure 18 and Figure 19.

Table 26: Key Secondary Endpoints in Study UX023-CL303 – Primary Analyses at Week 24

Visit	Worst Pain, by BPI			WOMAC Physical Function			WOMAC Stiffness	
Statistics	Placebo	Burosumab		Placebo	Burosumab		Placebo	Burosumab
Baseline, n	66	68		66	68		66	68
Mean (SD)	6.54 (1.433)	6.81 (1.308)		43.89 (19.938)	50.79 (19.660)		61.36 (20.770)	64.71 (20.253)
Week 24, n	65	67		65	66		65	67
Mean (SD)	6.09 (2.013)	5.82 (1.916)		42.65 (22.760)	43.43 (19.507)		60.38 (21.827)	53.73 (20.759)
LS Mean (SE) Change from Baseline[a]	-0.32 (0.222)	-0.79 (0.211)		+1.79 (2.722)	-3.11 (2.553)		+0.46 (3.139)	-7.85 (3.034)
LS Mean (SE) Difference[a]	-0.46 (0.275)			-4.90 (2.479)			-8.31 (3.251)[b]	
p-value Between Groups[a]	0.0919			0.0478			0.0106[b]	
Significance Level for Test	0.05			0.025			0.0167	
Significant?	No			No			Yes	

a: The estimates of LS means and p-values at Week 24 are from the GEE model, which includes the change from Baseline for the endpoint of interest as the dependent variable, region, visit, treatment, actual randomisation stratification (not included for analysis of BPI Worst Pain), and visit by treatment as fixed factors, and Baseline value for the endpoint of interest as a covariate, with compound symmetry covariance structure
b: WOMAC Stiffness subscale score at Week 24 was re-analysed for the Week 48 CSR; the values for LS mean, SE, and p-value changed from the original report, but the statistical significance did not change (see UX023-CL303 Week 48 CSR Section 8.8.5.6.1).
BPI = Brief Pain Inventory; GEE = generalised estimation equation; LS = least squares; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities osteoarthritis index

Figure 16: Least Squares Mean (± SE) Change From Baseline in BPI Worst Pain Scores Over Time (Primary Analysis Set)

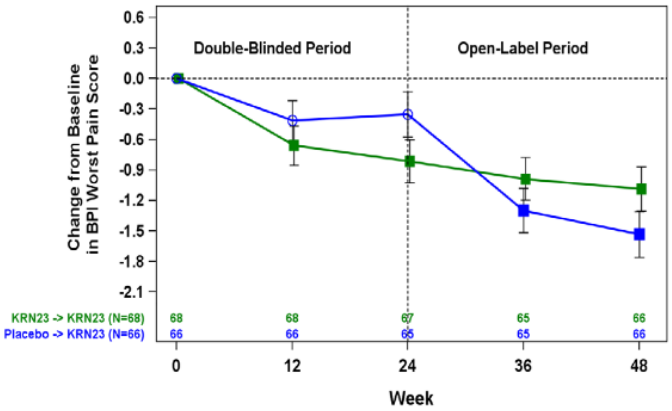


Figure 17: Least Squares Mean (± SE) Change from Baseline in WOMAC Physical Function Score Over Time (Primary Analysis Set)

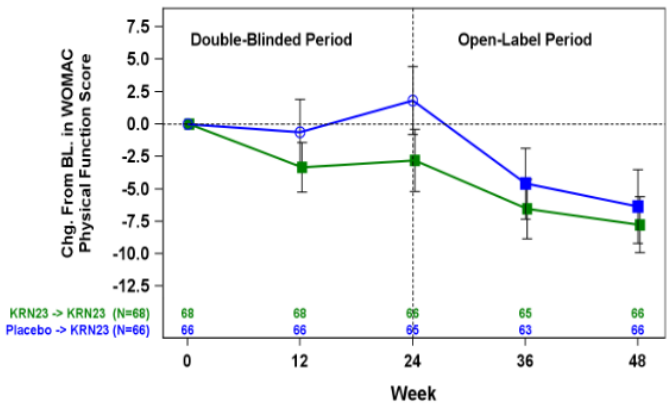
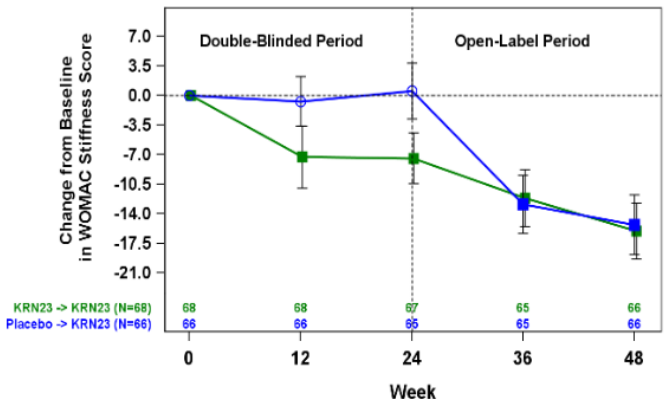


Figure 18: Least Squares Mean (± SE) Change from Baseline in WOMAC Stiffness Score Over Time (Primary Analysis Set)



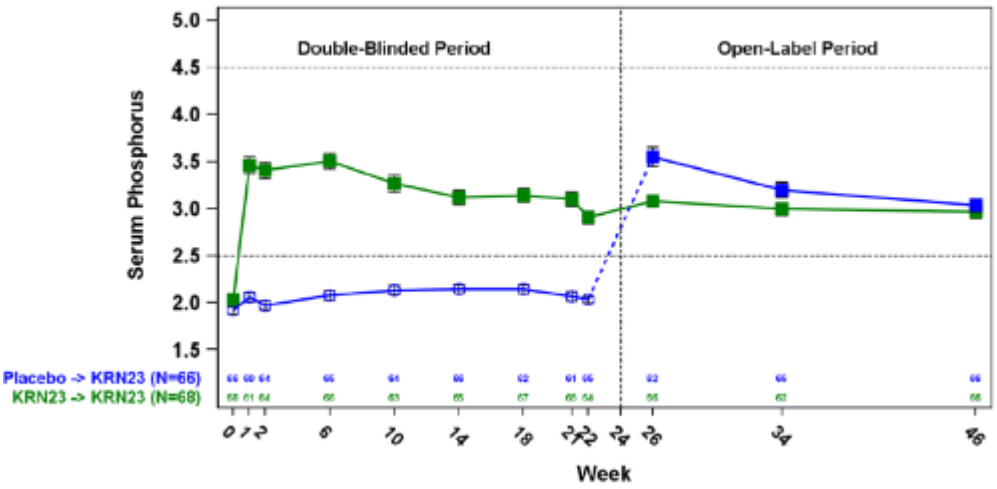
For Figure 17 to Figure 19, the following legend applies:

Other Secondary endpoints: Serum phosphate

In the burosumab group 67.6% achieved a mean serum phosphorus concentration above the LLN across the ends (time of trough PD effect) of the dose intervals through Week 24 compared to 6.1%.

Results of secondary analyses assessing additional changes in serum phosphorus at both the midpoints (time of peak PD effect) of the dose cycles is shown in Figure 20. All subjects received burosumab beginning at the Week 24 visit; however, they remained blinded to their previous treatment assignment.

Figure 19: Mean (± SE) Serum Phosphorus Peak Concentrations (mg/dL) Over Time in Study UX023-CL303 KRN23



Detailed information on secondary phosphate endpoints are summarised in Table 29.

Table 27: Serum Phosphorus Secondary Analyses (Primary Analysis Set) UX023-CL303

	Placebo-controlled Treatment Period (Weeks 0 – 24)		Treatment Continuation Period (Weeks 24 – 48)	
Parameter Statistics	**Placebo (N = 66)**	**Burosumab (N = 68)**	**Placebo→ Burosumab (N = 66)**	**Burosumab→ Burosumab (N = 68)**
Baseline Mean (SD) Serum Phosphorus, mg/dL	1.92 (0.316)	2.03 (0.304)	-	-
Serum Phosphorus Across the Midpoints of Dose Cycles				
Mean (SD), mg/dL	2.08 (0.298)	3.24 (0.532)	3.24 (0.552)	3.02 (0.475)
Mean Change (SD) from Baseline, mg/dL	0.16 (0.272)	1.21 (0.510)	1.32 (0.511)	0.99 (0.465)
Mean Percentage Change (SD) from Baseline, %	9.85 (15.292)	61.43 (28.835)	71.53 (32.357)	50.88 (28.504)
> LLN Across the Midpoints of the Dose Intervals - n (%)	5 (7.6)[a]	64 (94.1)[a]	59 (89.4)	57 (83.8)
95% CI[b]	(3.3, 16.5)	(85.8, 97.7)	(79.7, 94.8)	(73.3, 90.7)
Serum Phosphorus Across the Ends of Dose Cycles				
Mean (SD), mg/dL	2.05 (0.302)	2.72 (0.448)	2.67 (0.462)	2.58 (0.420)
Mean Change (SD) from Baseline, mg/dL	0.13 (0.265)	0.69 (0.392)	0.75 (0.437)	0.54 (0.420)
Mean Percentage Change (SD) from Baseline, %	7.83 (14.755)	35.21 (20.704)	41.15 (26.334)	28.28 (21.559)
> LLN Across the Ends of the Dose Intervals - n (%)	4 (6.1)	46 (67.6)	-	-
95% CI[b]	(2.4, 14.6)	(55.8, 77.6)	-	-
Serum Phosphorus at End of Period (Week 24 or Week 48)				
Mean (SD) Serum Phosphorus, mg/dL	2.07 (0.343)	2.53 (0.446)	2.47 (0.494)	2.47 (0.455)
Mean Change (SD) from Baseline, mg/dL	0.15 (0.346)	0.49 (0.395)	0.54 (0.482)	0.44 (0.454)
LS Mean Change (SE) from Baseline, mg/dL[c]	0.00 (0.070)	0.40 (0.083)	0.40 (0.081)	0.35 (0.079)
Mean Percentage Change (SD) from Baseline, %	9.20 (19.309)	25.38 (20.181)	30.28 (27.087)	23.32 (23.527)
LS Mean Percentage Change (SE) from Baseline, %[c]	0.38 (3.632)	21.17 (4.105)	21.45 (4.191)	18.73 (3.946)
Serum Phosphorus AUC, mg/dL	2.08 (0.292)	3.08 (0.475)	2.91 (0.473)	2.80 (0.426)

Other Secondary Endpoints Assessing PROs

The PROs included in the Secondary endpoints (Change from Baseline to post-Baseline visits) were BPI Worst Pain, BPI Pain severity, BPI Pain interference, BFI Worst Fatigue, BFI Global Fatigue, WOMAC Stiffness, and WOMAC Physical Function.

At Week 24, the BPI Pain Severity score in the burosumab had decreased from 5.2 at baseline to 4.4 at Week 24. The corresponding numbers for placebo was 4.9 to 4.6. The LS mean difference between the treatment arms was -0.4 [0.25] (p = 0.093).

At week 24, the BPI Pain Interference in the burosumab had decreased from 5.2 at baseline to 4.4 at Week 24. The corresponding numbers for placebo was 4.7 to 4.2. The LS mean difference between the treatment arms was -0.13 [0.29] (p = 0.65).

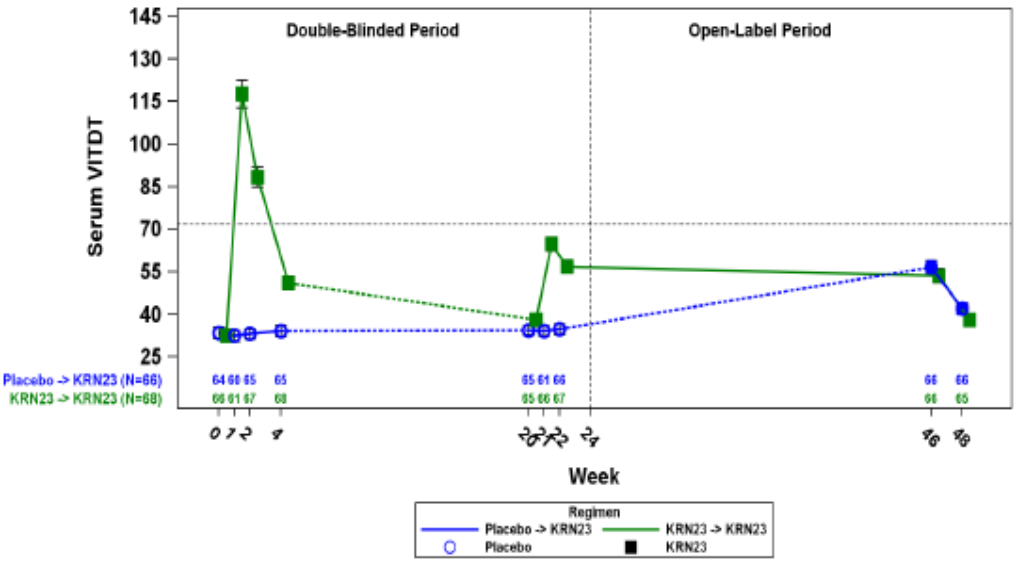
At week 24, the BFI Worst Fatigue, in the burosumab had decreased from 6.9 at baseline to 6.0 at Week 24. The corresponding numbers for placebo was 6.7 to 6.1. The LS mean difference between the treatment arms was -0.20 [0.31] (p = 0.52).

At week 24, the BFI Global Fatigue, in the burosumab had decreased from 5.3 at baseline to 4.7 at Week 24. The corresponding numbers for placebo was 4.8 to 4.2. The LS mean difference between the treatment arms was +0.11 [0.29] (p = 0.71).

Other Secondary Efficacy Endpoints – Pharmacodynamic Measures

Serum 1,25(OH)2D concentrations increased after initiation of burosumab treatment, which was an expected PD effect (Figure 21).

Figure 20: Mean (± SE) Serum 1,25(OH)2D Concentrations (pg/mL) over Time in Study UX023-CL303

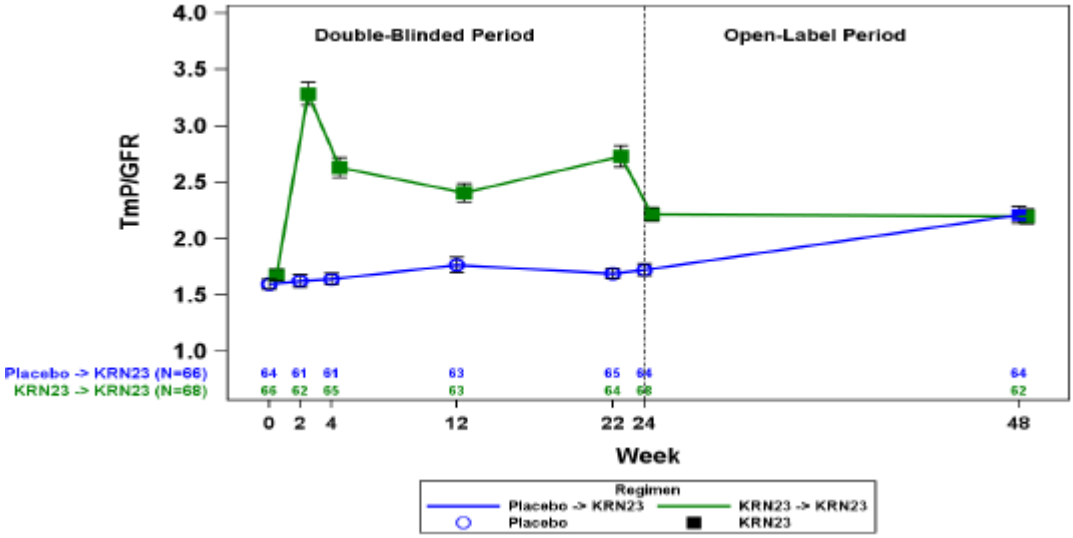


The horizontal line represents the upper limit of normal.

The LS mean (SE) difference between treatment groups in the change from Baseline to Week 22 (22.7 [2.40] pg/mL) was significant (p < 0.0001), as was the difference in percentage change (81.6% [11.67%]) (p < 0.0001).
The feedback regulation of serum 1,25(OH)2D levels over time has been observed in all burosumab studies and likely represents normal feedback regulation as phosphate-calcium homeostasis improves with burosumab therapy.

The ratio of renal tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR) is presented in Figure 22.

Figure 21: Mean (± SE) TmP/GFR over Time in Study UX023-CL303



At Week 24, the LS mean (SE) change from Baseline to Week 24 was 0.56 (0.110) mg/dL in the burosumab group and 0.13 (0.090) mg/dL in the placebo group (LS mean [SE] difference 0.43 [0.067] mg/dL; $p < 0.0001$).

Increases in TmP/GFR due to burosumab were accompanied by increases in tubular reabsorption of phosphate (TRP). The mean (SD) TRP at Baseline was 0.81 (0.083) for the burosumab group and 0.81 (0.084) for the placebo group. At Week 24, mean (SD) was 0.84 (0.065) for the burosumab group and 0.80 (0.106) for the placebo group (LS mean [SE] difference in the change from Baseline 0.04 [0.013]; $p = 0.0008$).

Bone biomarkers in serum reflect the rate of bone remodelling. With osteomalacia, a hallmark of XLH (Glorieux et al. 1980), (Sullivan et al. 1992), the poorly mineralized bone prevents osteoclasts from attaching to the bone surface to initiate the bone remodelling process. Therefore, patients with XLH have a low bone remodelling rate that impairs bone quality, leading to pseudofractures and delayed fracture healing.

P1NP and CTx are markers of bone formation and bone resorption, respectively. ALP and BALP are important markers in XLH-related bone disease in the paediatric population but are less indicative of bone disease in the adult population. In addition, ALP and BALP are less sensitive to changes in bone remodelling than P1NP and CTx

The effect of burosumab on P1NP, and CTx are summarised in Figure 23 and Figure 24,respectively.

Figure 22: Mean (± SE) Serum P1NP (ng/mL) Concentration Over Time in Study UX023-CL303

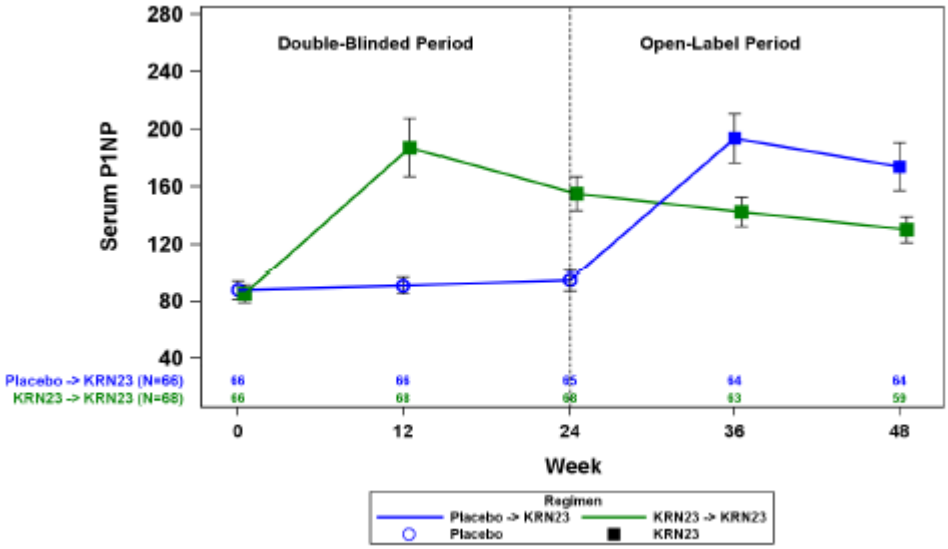
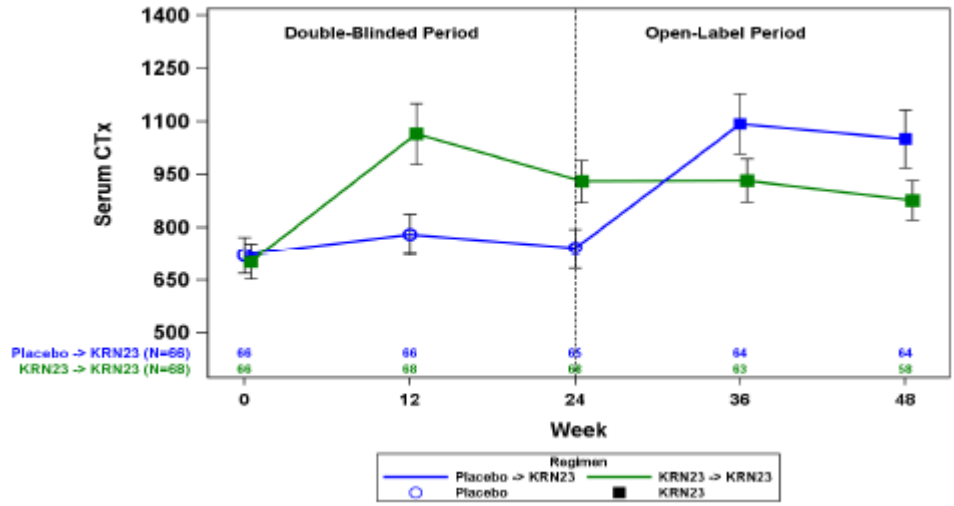


Figure 23: Mean (± SE) Serum CTx (pg/mL) Concentration Over Time in Study UX023-CL303



The mean (SD) P1NP concentration at Baseline was 85 (50.7) ng/mL in the burosumab group and 88 (53.3) ng/mL in the placebo group. At Week 24, the LS mean (SE) differences between treatment groups for the change from Baseline (62 [7.5] ng/mL) and for the percentage change from Baseline (65.5% [8.1%]) were both statistically significant ($p < 0.0001$ for each).

The mean (SD) CTx concentration at Baseline was 702 (395.5) pg/mL in the burosumab group and 721 (417.9) pg/mL in the placebo group At Week 24, the LS mean (SE) differences between treatment groups for the change from Baseline (190 [41.2] pg/mL) and for the percentage change from Baseline (27.5% [7.4%]) were both statistically significant ($p \leq 0.0002$).

For BALP, no statistically significant difference in change from baseline between the treatment arms was reported (LS mean [SE increase] 41.2% [11.4%] vs 31.1% [10.9%]; $p = 0.4574$).

Exploratory Efficacy Endpoints: Pseudofracture and Fracture Healing as Defined by Skeletal Survey

The MAH contracted a third party to provide an independent review of site-acquired x-ray data. One independent reviewer was to review the baseline skeletal survey x-rays and indicate if there are active or non-active bone fractures and pseudo-fractures and their locations. Two different independent reviewers

assessed the targeted x-ray time point images, comparing the current time point image with the image from the baseline time point or the time point the fracture was initially identified.

However ,during analysis of the radiograph data for this study, it was discovered that at least 1 of the 2 trained central readers did not consistently use the Baseline radiograph as the comparator for grading purposes as intended and instead used the most recent radiograph as the comparator (e.g., the Week 12 radiograph was used as the comparator to determine Week 24 fracture/pseudofracture healing grading). In this context, the Week 12 fracture/pseudofracture grading results are valid because Baseline was the only possible comparator. Also, because a healed grade (reflecting complete healing) has a strict definition that is independent of comparator and not subject to bias, the numbers of fractures/pseudofractures reported as healed at Week 24 are valid and reliable; however, fractures/pseudofractures reported to be partially healed, unchanged, or worse at Week 24 may not be accurate in some cases given the inconsistent use of the Baseline X-ray as a comparator.

Analyses described in the primary report, therefore, focused primarily on: (1) the percentages of Baseline active fractures and pseudofractures that are healed (completely) at Weeks 12 and 24 and (2) ad hoc estimation of an odds ratio for active fracture and pseudofracture healing based on a generalized linear mixed proportional odds model for binary responses While both of these approaches are valid in this context, Week 24 radiographs were also re-read after a central reader re-training to confirm the results of the Week 24 analyses. The results of the re-read are provided in this report. As the imaging vendor platform required readers to simultaneously enter fracture grades and calcaneal enthesopathy measurements, the Week 24 calcaneal enthesopathy measurements were re-read as well. The goal of the re-read was to provide a full and accurate fracture healing dataset. Readers and imaging vendor personnel remained blinded to double-blind treatment assignment of the subjects. Readers did not have access to their previous Week 24 grading scores.

At baseline, 32 (47%) subjects in the burosumab group had a total of 14 active fractures and 51 active pseudofractures; 38 (58%) subjects in the placebo group had at total of 13 active fractures and 78 active pseudofractures.

The percentage of Baseline active fractures/pseudofractures for each grade (re-read) is summarised in Table 30.

Table 28: Active Fractures and Pseudofractures over Time in Study UX023-CL303

Number of Active Fracture/ Pseudofractures	Active Fractures		Active Pseudofractures		Total	
	Placebo (N = 66)	Burosumab (N = 68)	Placebo (N = 66)	Burosumab (N = 68)	Placebo (N = 66)	Burosumab (N = 68)
Baseline	13	14	78	51	91	65
Week 12 grade – n (% baseline)						
Healed	0	2 (14.3)	7 (9.0)	11 (21.6)	7 (7.7)	13 (20.0)
Partially Healed	2 (15.4)	8 (57.1)	22 (28.2)	18 (35.3)	24 (26.4)	26 (40.0)
Unchanged	11 (84.6)	3 (21.4)	26 (33.3)	13 (25.5)	37 (40.7)	16 (24.6)
Worse	0	0	10 (12.8)	0	10 (11.0)	0
Missing	0	1 (7.1)	13 (16.7)	9 (17.6)	13 (14.3)	10 (15.4)
New Finding	2	0	6	3	8	3
Week 24 grade – n (% baseline)						
Healed	0	7 (50.0)	7 (9.0)	21 (41.2)	7 (7.7)	28 (43.1)
Partially Healed	6 (46.2)	3 (21.4)	19 (24.4)	13 (25.5)	25 (27.5)	16 (24.6)
Unchanged	2 (15.4)	3 (21.4)	39 (50.0)	6 (11.8)	41 (45.1)	9 (13.8)
Worse	3 (23.1)	0	8 (10.3)	2 (3.9)	11 (12.1)	2 (3.1)
Missing	2 (15.4)	1 (7.1)	5 (6.4)	9 (17.6)	7 (7.7)	10 (15.4)
New Finding	0	1	0	2	0	3
	Placebo→ Burosumab	Burosumab→ Burosumab	Placebo→ Burosumab	Burosumab→ Burosumab	Placebo→ Burosumab	Burosumab→ Burosumab
Week 36 grade – n (% baseline)						
Healed	3 (23.1)	7 (50.0)	18 (23.1)	26 (51.0)	21 (23.1)	33 (50.8)
Partially Healed	3 (23.1)	2 (14.3)	29 (37.2)	9 (17.6)	32 (35.2)	11 (16.9)
Unchanged	3 (23.1)	4 (28.6)	14 (17.9)	5 (9.8)	17 (18.7)	9 (13.8)
Worse	2 (15.4)	0	3 (3.8)	2 (3.9)	5 (5.5)	2 (3.1)
Missing	2 (15.4)	1 (7.1)	14 (17.9)	9 (17.6)	16 (17.6)	10 (15.4)
New Finding	0	0	2	1	2	1
Week 48 grade – n (% baseline)						
Healed	6 (46.2)	8 (57.1)	26 (33.3)	33 (64.7)	32 (35.2)	41 (63.1)
Partially Healed	4 (30.8)	2 (14.3)	32 (41.0)	9 (17.6)	36 (39.6)	11 (16.9)
Unchanged	1 (7.7)	2 (14.3)	10 (12.8)	4 (7.8)	11 (12.1)	6 (9.2)
Worse	0	0	0	0	0	0
Missing	2 (15.4)	2 (14.3)	10 (12.8)	5 (9.8)	12 (13.2)	7 (10.8)
New Finding	1	0	0	0	1	0

A post hoc analysis using a hierarchical generalised linear mixed proportional odds model was performed separately at Weeks 12, 24, 36, and 48 to estimate the probabilities of fracture grade occurrence and odds ratios for healed fractures and their 95% CIs (Table 31).

Table 29: Post Hoc Analysis of Active Fractures and Active Pseudofractures Grades in Study UX023-CL303

	Placebo (N = 66)	Burosumab (N = 68)
Number Active Fracture/Pseudofractures at Baseline	91	65
Week 12 Grade		
Healed, probability	0.050	0.167
Odds Ratio Burosumab vs Placebo (95% CI)	3.84 (1.06. 13.89)	
Between-group p-value	0.0403	
Week 24 Grade		
Healed, probability	0.048	0.458
Odds Ratio Burosumab vs Placebo (95% CI)	16.76 (4.93, 56.95)	
Between-group p-value	<0.0001	
	Placebo→ Burosumab	Burosumab→ Burosumab
Week 36 Grade		
Healed, probability	0.234	0.568
(95% CI)	(0.069, 0.399)	(0.318, 0.819)
Week 48 Grade		
Healed, probability	0.386	0.725
(95% CI)	(0.178, 0.594)	(0.516, 0.933)
P-value (vs zero probability of healing)	0.0003	<0.0001

Probabilities of each fracture grade occurrence, odds ratios at each visit, and their confidence intervals are estimated using a generalised linear mixed model for binomial distribution that includes treatment, visit, treatment by visit, and fracture type as fixed factors, accounting for nesting of fractures within subjects.
CI = confidence interval.

Exploratory Efficacy Endpoints: Enthesopathy Burden as Defined by Skeletal Survey

Mineralization of tendons/ligaments (enthesopathy) is a feature of XLH that can contribute to stiffness. Total calcaneal enthesopathy burden was assessed as the sum of dimensions of superior and inferior calcaneal spurs bilaterally measured in 2 dimensions; measured by lateral foot X-rays. Because this assessment was added in Protocol Amendment 1, approximately 9 months after enrolment of the first subject, few subjects completed this assessment at both Baseline and at Week 24 (12 burosumab, 10 placebo). Greater numbers of subjects completed this assessment at both Baseline and Week 48 (52 burosumab, 45 placebo).

Enthesopathy was present in nearly all subjects (99.3%) at baseline (Table 32).

Table 30: Change from Baseline to Week 48 in mean Total Calcaneal Enthesopathy Burden Measured by Lateral Foot X-Rays (cm) Primary Analysis Set UX023-CL303 (compiled by Assessor)

Visit	Placebo (N=66)	Burosumab (N=68)
Baseline		
n	52	59
Enthesopathy burden (cm/[SD])	5.54 (3.09)	5.64 (3.12)
Week 24		
n	10	12
Baseline Enthesopathy burden (cm/[SD]) for observed subjects	5.05 (3.37)	6.08 (2.92)
Enthesopathy burden (cm/[SD])	4.07 (2.38)	5.90 (3.17)

Week 48		
n	45	52
Baseline Enthesopathy burden (cm/[SD]) for observed subjects	5.97 (3.05)	5.63 (3.06)
Enthesopathy burden (cm/[SD])	5.99 (3.06)	5.25 3.03

The ANCOVA Estimates from the ANCOVA model which includes the change from baseline in total calcaneal enthesopathy burden measured by lateral foot x-rays as the dependent variable, treatment, actual randomization stratification based on BPI average pain as fixed factors and baseline of total calcaneal enthesopathy burden as a covariate are presented below:

Table 31: Analysis of Change from Baseline to Week 24 in mean Total Calcaneal Enthesopathy Burden Measured by Lateral Foot X-Rays (cm) Primary Analysis Set UX023-CL303

Visit	Statistics	Placebo (N=66)	KRN23 (N=68)
Week 24	ANCOVA Estimates		
	LS Mean (SE)	-1.55 (0.704)	-0.47 (0.638)
	95% CI	(-3.03, -0.07)	(-1.81, 0.87)
	LS Mean Difference (SE)		1.08 (0.923)
	95% CI		(-0.86, 3.02)
	p-value		0.2577

At Week 48, the LS mean (SE) change from Baseline to Week 48 was -0.53 (0.208) cm in the burosumab→burosumab group and -0.12 (0.224) cm in the placebo→burosumab group.

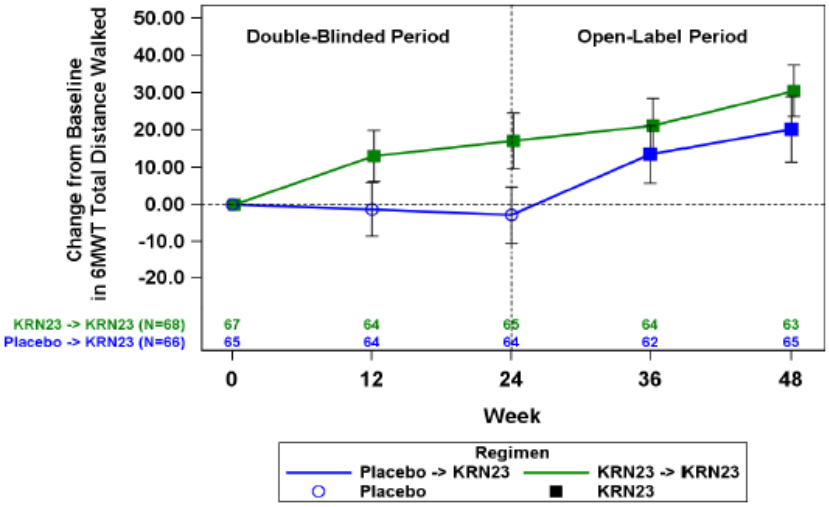
Exploratory Efficacy Endpoints: Mobility by 6MWT

At Baseline, the mean (SD) actual distance walked was 356.8 (109.46) m (range: 55 – 643 m) in the burosumab group and 367.4 (103.41) m (160 – 615 m) in the placebo group.

Change from baseline in distance walked in 6MWT (m) is shown in Figure 25. At Week 24, the LS mean (SE) change from Baseline was 14.8 (7.67) m in the burosumab group and -5.0 (7.54) m in the placebo group; the LS mean difference between treatment groups was 19.8 (7.67) m (p = 0.0108).

The LS mean (SE) change from Baseline to Week 48 was 30.5 (6.93) m in the burosumab→burosumab group and 20.2 (8.76) m in the placebo→burosumab group.

Figure 24: Least Squares Mean (± SE) Change from Baseline in Distance Walked in 6MWT (m) and in StucharL8Mdy UX023-CL303



Exploratory endpoint: Timed up and go test (TUG)

TUG was added in Protocol Amendment 1, approximately 9 months after enrolment of the first subject No baseline values are recorded and only a small subset of subjects has records from Week 24 (4 burosumab, 5 placebo). At Week 48, TUG was recorded in 32 subjects in each treatment arm.

Exploratory Efficacy Endpoints: Patient Global Impression of Improvement

The Patient Global Impression of Severity (PGI-S) and Patient's Global Impression of Improvement (PGI-I) instruments were administered to assess subject perception of disease severity at baseline and improvement with treatment over time, respectively.

The mean (SD) PGI-S score at Baseline on a scale of 1 (normal) to 4 (severe) was 3.2 (0.62) in the burosumab group and 3.0 (0.82) in the placebo group.

At Week 24, the LS mean (SE) PGI-I score on a scale from 1 (very much better) to 7 (very much worse) was 3.6 (0.16) in the burosumab group and 3.9 (0.17) in the placebo group (LS mean [SE] difference -0.3 [0.23]; p = 0.2035).

Summary of main study(ies)

The following table (Table 34) summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32: Summary of efficacy for study UX023-CL303

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)		
Study identifier	UX023-CL303	
Design	Ongoing, randomized, double-blind, placebo-controlled, multicenter, Phase 3 study with open-label treatment continuation and treatment extension periods	
	Duration of main phase (placebo-controlled):	24 weeks
	Duration of treatment continuation phase (open-label):	24 weeks
Hypothesis	Superiority	
Treatment groups	Placebo-controlled treatment period (24 weeks)	Burosumab 1 mg/kg via SC injection Q4W Placebo to match

	Treatment continuation period (24 weeks)		Burosumab 1 mg/kg via SC injection Q4W
Endpoints and definitions	Primary endpoint	Serum phosphorus levels	The proportion of subjects achieving mean serum phosphorus levels above the LLN (2.5 mg/dL [0.81 mmol/L]) at the midpoint of the dose interval (i.e., Weeks 2, 6, 10, 14, 18, and 22), as averaged across dose cycles between Baseline and Week 24.
	Key secondary	BPI Worst Pain score	Change from baseline to Week 24 (scale 1-10)
	Key secondary	WOMAC Stiffness score	Change from baseline to Week 24 (scale 1-100)
	Key secondary	WOMAC Physical Function score	Change from baseline to Week 24 (scale 1-100)
Database lock	23 March 2017 (Week 24), 25 October 2017 (Week 48)		
Results and Analysis			
Analysis Description	**Primary Analysis**		
Analysis population and time point description	Primary analysis set: all randomised subjects who received at least 1 dose of study drug during the placebo-controlled treatment period. Subjects were analyzed according to the randomized treatment group, regardless of the actual treatment received. 22 December 2016 (Week 24 data cut-off date) 08 June 2017 (Week 48 data cut-off date)		

Descriptive statistics and estimate variability

Primary Endpoint		
Treatment Group	Placebo	Burosumab
Number of subjects	66	68
Proportion of subjects who achieved mean serum phosphorus >LLN across midpoints of dose intervals through Week 24	5 (7.6%)	64 (94.1%)
95% CI	3.3, 16.5	85.8, 97.7
P-value	<0.0001	

Key Secondary Endpoints

BPI Worst Pain change

	Week 24		Week 48	
	Placebo	Burosumab	Placebo> Burosumab	Burosumab> Burosumab
Number of subjects	65	67	66	66
Mean change from baseline (SE)	-0.42 (0.218)	-0.98 (0.191)	-1.64 (0.227)	-1.26 (0.212)

WOMAC Stiffness score

	Week 24		Week 48	
	Placebo	Burosumab	Placebo> Burosumab	Burosumab> Burosumab
Number of subjects	65	67	66	68
Mean change from baseline (SE)	-0.77 (2.698)	-10.63 (2.987)	-16.67 (3.081)	-19.32 (3.103)

WOMAC Physical Function score

	Week 24	Week 48

<table>
<tr><td></td><td></td><td>Placebo</td><td>Burosumab</td><td>Placebo> Burosumab</td><td>Burosumab> Burosumab</td></tr>
<tr><td></td><td>Number of subjects</td><td>65</td><td>66</td><td>66</td><td>66</td></tr>
<tr><td></td><td>Mean change from baseline (SE)</td><td>-0.97 (1.826)</td><td>-6.90 (1.886)</td><td>-9.16 (2.230)</td><td>-11.96 (1.855)</td></tr>
<tr><td>Effect estimate per comparison</td><td colspan="5">Week 24</td></tr>
<tr><td></td><td>Key secondary BPI Worst Pain change at Week 24</td><td colspan="2">Comparison groups</td><td colspan="2">Burosumab-Placebo</td></tr>
<tr><td></td><td></td><td colspan="2">LS mean (SE) difference</td><td colspan="2">-0.46 (0.275)</td></tr>
<tr><td></td><td></td><td colspan="2">P-value</td><td colspan="2">0.0919</td></tr>
<tr><td></td><td>Key secondary WOMAC Physical Function score at Week 24</td><td colspan="2">Comparison groups</td><td colspan="2">Burosumab-Placebo</td></tr>
<tr><td></td><td></td><td colspan="2">LS mean (SE) difference</td><td colspan="2">-4.90 (2.479)</td></tr>
<tr><td></td><td></td><td colspan="2">P-value</td><td colspan="2">0.0478</td></tr>
<tr><td></td><td>Key secondary WOMAC Stiffness score at Week 24</td><td colspan="2">Comparison groups</td><td colspan="2">Burosumab-Placebo</td></tr>
<tr><td></td><td></td><td colspan="2">LS mean (SE) difference</td><td colspan="2">-8.31 (3.251)</td></tr>
<tr><td></td><td></td><td colspan="2">P-value</td><td colspan="2">0.0106</td></tr>
<tr><td></td><td colspan="5">Week 48</td></tr>
<tr><td></td><td>Key secondary BPI Worst Pain change</td><td>Comparison groups</td><td>Placebo> Burosumab</td><td>Burosumab> Burosumab</td></tr>
<tr><td></td><td></td><td>LS mean (SE) change</td><td>-1.53 (0.228)</td><td>-1.09 (0.216)</td></tr>
<tr><td></td><td></td><td>P-value</td><td><0.0001</td><td><0.0001</td></tr>
<tr><td></td><td>Key secondary WOMAC Stiffness score</td><td>Comparison groups</td><td>Placebo> Burosumab</td><td>Burosumab> Burosumab</td></tr>
<tr><td></td><td></td><td>LS mean (SE) change</td><td>-15.29 (3.542)</td><td>-16.03 (3.315)</td></tr>
<tr><td></td><td></td><td>P-value</td><td><0.0001</td><td><0.0001</td></tr>
<tr><td></td><td>Key secondary WOMAC Physical Function score</td><td>Comparison groups</td><td>Placebo> Burosumab</td><td>Burosumab> Burosumab</td></tr>
<tr><td></td><td></td><td>LS mean (SE) change</td><td>-6.35 (2.851)</td><td>-7.76 (2.146)</td></tr>
<tr><td></td><td></td><td>P-value</td><td>0.0259</td><td>0.0003</td></tr>
<tr><td>Analysis description</td><td colspan="5">The primary efficacy endpoint was analysed using the Cochran-Mantel-Haenszel (CMH) test to compare the percentages of subjects in the burosumab and placebo groups who achieved a serum phosphorus level above the LLN (2.5 mg/dL [0.81 mmol/L]) at the midpoint of the dosing interval, as averaged across dose cycles between Baseline and Week 24, adjusting for the actual stratification factors used for randomization (BPI Average Pain [> 6.0 or ≤ 6.0] and region [North America/EU, Japan, South Korea]). The primary endpoint was tested at the two-sided alpha level of 0.05.</td></tr>
</table>

Supportive study(ies)

UX023-CL203

Study Title

A Phase 2b, Open-Label, Long-Term Extension Study to Evaluate the Safety and Pharmacodynamics of KRN23 in Adult Subjects with X-Linked Hypophosphatemia (XLH)

Study Design

This ongoing, open-label extension study enrolled adults with XLH who previously participated in Study KRN23-INT-001 or KRN23-INT-002 to collect additional information on the safety, PD response,

immunogenicity, Patient reported outcomes (PROs), and mobility with long-term SC administration of burosumab in this subject population.

Subjects who were discontinued from Study KRN23-INT-001 or KRN23-INT-002 due to a treatment-emergent adverse event classified as possibly or probably related to treatment could be eligible for participation in this study based on the clinical judgment of the investigator with agreement from the applicant. The planned study duration is 194 weeks.

Treatments

All subjects received open-label 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.

Up to Week 12, if the subject had not reached serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL [0.81 mmol/L]) at the end of the dose interval, the investigator could titrate the dose upward every 4 weeks to a maximum dose of 1.0 mg/kg based on fasting trough serum phosphorus levels. Doses could be titrated downward if at any point the serum phosphorus level increased above the upper limit of normal (ULN; 4.5 mg/dL [1.45 mmol/L]).

Endpoints

The primary PD endpoints were:

- Number and percentage of subjects who had serum phosphorus levels in the normal range (2.5–4.5 mg/dL [0.81–1.45 mmol/L]) or outside the normal range.
- Change from Baseline in serum biochemistry parameters associated with XLH, as measured by serum phosphorus, iPTH, FGF23 (total and free), and 1,25(OH)2D.
- Change from Baseline in urinalysis parameters associated with XLH, as measured by 2-hour urine (ie, TmP/GFR, TRP, calcium, creatinine, phosphorus) and by 24-hour urine (ie, urinary phosphate, calcium, creatinine, urine calcium/creatinine ratio).
- Change from Baseline in bone biomarkers, as measured by total ALP and BALP, CTx, and P1NP.

The exploratory efficacy endpoints were:

- Change from Baseline in pain, stiffness, physical and mental functioning, and HRQoL as measured by changes in the WOMAC, BPI-SF, and SF-36v2 scores.
- Healing of prior or existing fractures or other disease-related skeletal abnormalities as viewed on standard radiographs.
- Change from Baseline in walking ability as measured by change in the distance walked on the 6MWT in meters and percent predicted normal values.
- Change from Baseline in transitions during ambulatory activity that incorporates strength, agility, and dynamic balance as measured by the time required to complete the Timed Up And Go (TUG) test.

Subject Disposition and Baseline Characteristics

All 20 (100.0%) enrolled subjects completed 48 weeks of burosumab administration. For further details, please refer to Table 16

Six (30%) subjects were male and 14 (70%) were female. The mean age was 49.8 years.

Notable findings on reported XLH medical history included short stature (95.0% of subjects), bowing of lower legs (95.0%), unusual gait (85.0%), dental abscess (85.0%), osteoarthritis (75.0%), enthesopathy

(60.0%), and nephrocalcinosis (20.0%). All subjects had joint stiffness/limited range of motion. Most subjects (85%) received prior phosphate or vitamin D treatment.

Exposure

At the Week 48 analysis cut-off date, subjects had received a median of 16.5 doses of burosumab (range, 13 [Week 48 dose] to 18 [Week 68 dose]).

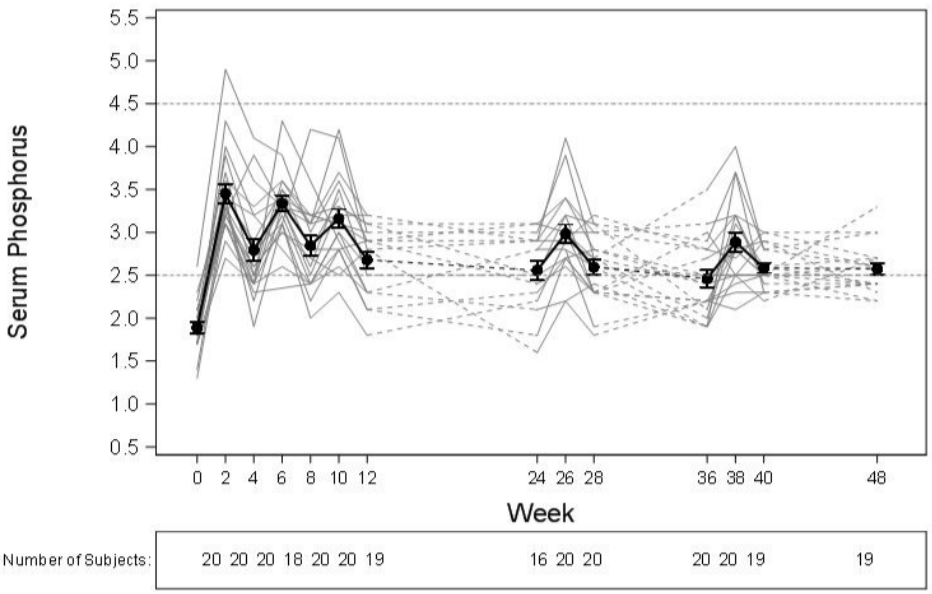
The median weight-based dose was 0.80 mg/kg at the Baseline visit and either 0.60 or 0.80 mg/kg at all post-Baseline visits through Week 48 of KRN23 treatment. Between Baseline and Week 48 of KRN23 treatment, 15 of 20 subjects received a stable dose throughout the study with most of these subjects receiving doses of 0.6 mg/kg (4/20 [20%]) or 1.0 mg/kg (9/20 [45%]). Three subjects who initiated treatment at a dose of 0.3 mg/kg increased their dose to 0.6 mg/kg at Week 4; one subject who initiated treatment at a dose of 0.6 mg/kg had a dose decrease to 0.3 mg/kg due to elevated serum phosphorus, and one subject who received a starting dose of 1.0 mg/kg had a dose reduction to 0.6 mg/kg followed by a return to the starting dose level at Week 24.

Results

Pharmacodynamics

The mean serum phosphorus concentration at baseline was below the normal range, as expected for subjects with XLH. Results from the pharmacodynamic parameters are summarised in Figure 26, Figure 27 and Figure 28.

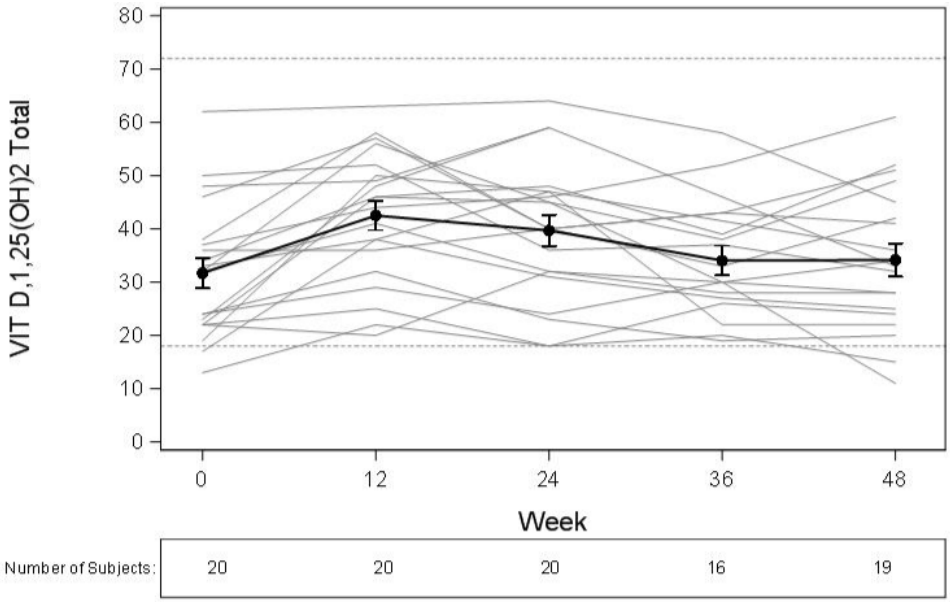
Figure 25: Individual and Mean (±SE) Serum Phosphorus Levels (mg/dL) (PD Analysis Set) UX023-CL203.



SE = standard error. Note: n = 16 at Week 24 because the laboratory cancelled four samples due to insufficient centrifugation. Dotted lines denote the range of normal for serum phosphorus, corresponding to 0.81-1.45 mmol/L.

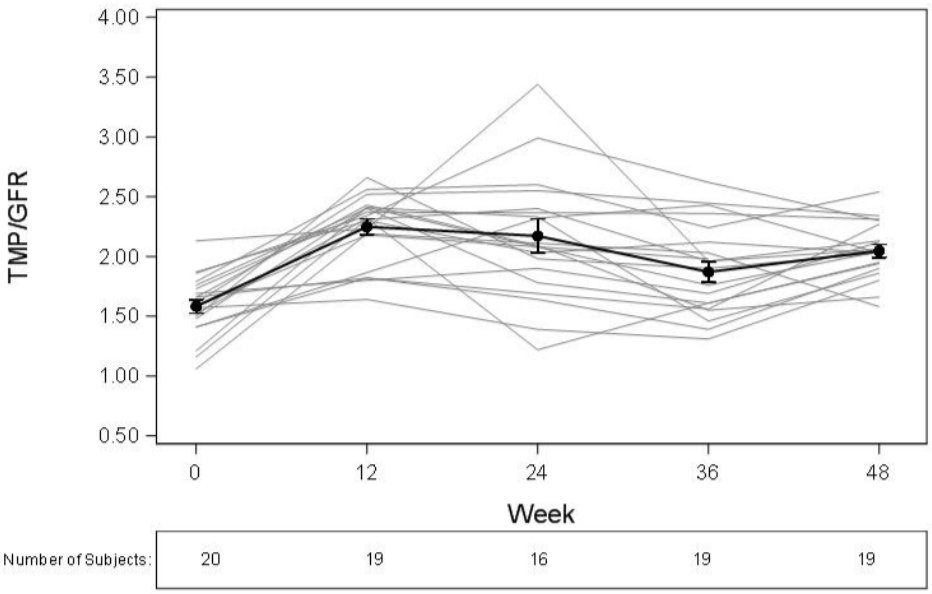
All 20 (100.0%) subjects had at least one serum phosphorus level in the normal range during burosumab dosing, including 85.0% to 100.0% of subjects at each midpoint visit 2 weeks after a dose (the time of peak PD effect), and 45.0% to 73.7% of subjects at trough visits just prior to the next dose, as expected from the monthly dosing regimen. LS mean change from baseline to Week 48 in serum phosphorus was 0.68 mg/dL [0.22 mmol/L] ($p<0.0001$).

Figure 26: Individual and Mean (±SE) Vitamin D - 1,25(OH)2D (pg/mL) (PD Analysis Set) UX023-CL203



LS mean change from baseline to Week 48 in Vitamin D - 1,25(OH)2D was 2.72 pg/mL (p=0.3119)

Figure 27: Individual and Mean (±SE) TmP/GFR (mg/dL) (PD Analysis Set) UX023-CL203.



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

LS mean change from baseline to Week 48 in Urinary 2-hour TmP/GFR was 0.46 mg/dL (p<0.0001).

Serum Bone Biomarkers

The effect of burosumab on the bone formation marker P1NP, the bone resorption marker CTx and the bone formation marker BALP are summarised in Figure 29.

Figure 28: Summary of PD Bone Biomarkers (PD Analysis Set) (UX023-CL203)

Visit Statistics	P1NP (ng/mL)	CTx (pg/mL)	ALP (U/L)	BALP (µg/L)
Baseline (n = 20)				
Mean (SD)	76.5 (41.58)	732.4 (404.01)	131.1 (50.50)	31.26 (18.528)
Week 24 (n = 20)				
Mean (SD)	149.0 (102.37)	1093.8 (704.70)	145.8 (60.18)	36.23 (23.069)
Mean (SD) Change From Baseline	+72.5 (79.28)	+339.0 (544.76)	+14.7 (25.69)	+3.65 (9.394)
LS Mean (SE) Percent Change From Baseline[a]	+102.3 (14.8)	+46.9 (11.5)	+11.4 (3.8)	+14.1 (5.9)
p-value[a]	< 0.0001	< 0.0001	0.0027	0.0174
Week 48 (n = 20)				
Mean (SD)	120.9 (50.99)	777.9 (317.11)	129.1 (47.28)	28.29 (16.567)
Mean (SD) Change From Baseline	+44.5 (32.88)	+45.5 (365.59)	-2.0 (28.56)	-2.97 (10.770)
LS Mean (SE) Percent Change From Baseline[a]	+72.5 (10.3)	+17.6 (7.7)	+0.9 (3.8)	-5.2 (4.6)
p-value[a]	< 0.0001	0.0214	0.8070	0.2615

Patient Reported Outcomes (PRO)

The MAH has provided data on BPI scores, WOMAC scores, SF-36v2 Physical components and SF-36v2 Mental components. With the exception of SF-36v2 Mental components, all scores showed a trend towards improvement with compared to baseline with burosumab treatment at week 24 and Week 48. None of the mental health domain scores of the SF-36v2 changed significantly from Baseline to Week 48 of KRN23 treatment.

Radiographic Endpoints

According to the MAH, analyses of postbaseline radiographic assessments will be provided separately in the final study report.

Mobility tests

The mean actual distance walked on the 6MWT increased from 322.4 m (range, 80.0–639.0 m) at Baseline to 352.0 m (range, 160.0–589.0 m) at Week 48 (LS mean change, 29.6 m; SE, 15.2; p = 0.0511).
Mean values for the "timed up and go test" (TUG) test decreased significantly from 12.8 sec (range, 6.2–24.9) at Baseline to 10.4 sec (range, 5.6–16.9) at Week 48 (LS mean change, -2.6 sec; SE, 0.6 sec p < 0.0001).

LS Mean change from Baseline in 6MWT is shown in Figure 30 and in TUG in Figure 31.

Figure 29: LS Mean (±SE) Change from Baseline in 6MWT (m) (Efficacy Analysis Set) UX023-CL203

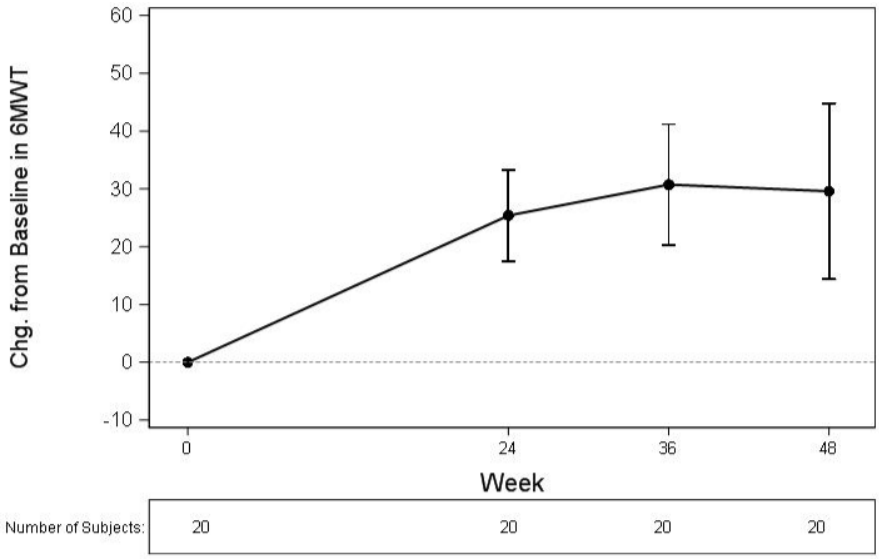
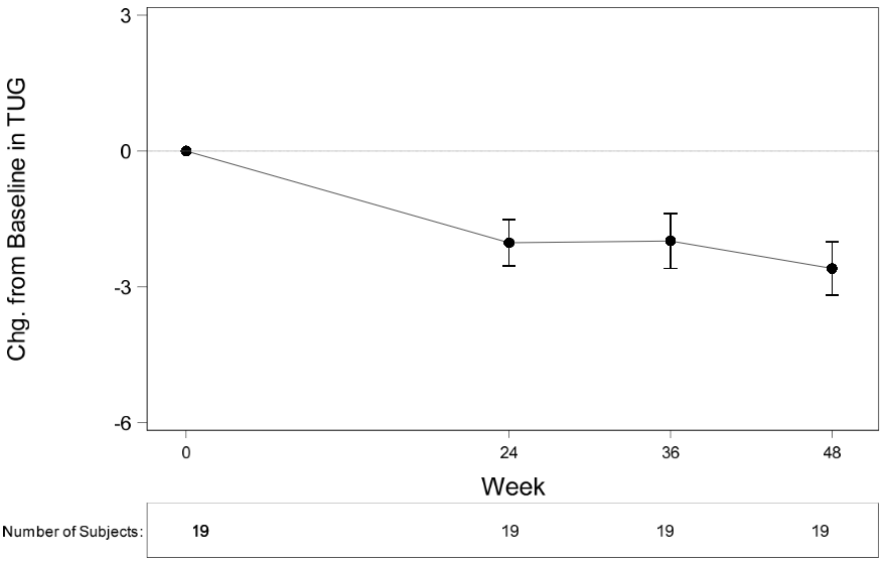


Figure 30: LS Mean (± SE) Change from Baseline in TUG (sec) Efficacy Analysis Set UX023-CL203



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)

Study Design

This ongoing, open-label, uncontrolled Phase 3 study was designed to establish the effects of burosumab on bone quality and osteomalacia associated with XLH.

The study enrolled adult subjects with a diagnosis of XLH supported by typical clinical and biochemical features and who had not received oral phosphate and vitamin D therapy in the 2 years prior to enrolment.

Burosumab, 1.0 mg/kg, was administered via SC injections Q4W for 48 weeks. Subjects who complete the study may participate in an open-label extension study.

Endpoints

- Primary Efficacy Endpoint
    - The percent change from Baseline in osteoid volume/bone volume (OV/BV) at Week 48 based on analysis of iliac crest bone biopsies.
- Key Secondary Efficacy Endpoint
    - The proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL [0.81 mmol/L]) at the mid-point of the dose interval (ie, Weeks 2, 6, 14, and 22), as averaged across dose cycles between Baseline and Week 24.
- Additional Secondary Efficacy Endpoints
    - Percent changes from Baseline in additional histomorphometric parameters – including osteoid thickness (O.Th), osteoid surface/bone surface (OS/BS), and mineralization lag time (MLt)
    - Changes from Baseline in MAR, MS/BS, BFR and additional measures of bone formation and remodelling
    - Additional measures to assess serum phosphorus levels between baseline and Week 24 include:
        - 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), as averaged across dose cycles
        - Mid-point of dosing cycle: mean change from Baseline and percent change from Baseline averaged across dose cycles
        - End of dosing cycle: mean change from Baseline, and percent change from Baseline averaged across dose cycles
        - Cumulative exposure: time-adjusted area under the curve (AUC)
    - Change from Baseline over time in 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)
    - Change and percent change from Baseline over time in serum biochemical markers of bone turnover, including procollagen type 1 N-propeptide (P1NP), carboxy-terminal cross-linked telopeptide of type I collagen (CTx), and bone-specific alkaline phosphatase (BALP)
- Exploratory Efficacy Endpoints:
    - Healing of active pseudofractures and/or fractures, as defined by skeletal survey at Baseline and subsequent targeted radiography
    - Change from Baseline in BPI Pain Severity and in Pain Interference scores over time
    - Change from Baseline over time in Brief Fatigue Inventory (BFI) Q3-Worst Fatigue Scores
    - Change from Baseline over time in BFI Global Fatigue Score, calculated by averaging all 9 items on the BFI

Subject Disposition and Baseline Characteristics

A total of 14 adult subjects have been enrolled into the study. As of the data cut-off date for the Week 48 analysis (30 Aug 2017), 13 subjects remained in the study and had completed the 48-week Open-label Treatment Period. One subject withdrew consent and discontinued from the study after 12 burosumab doses prior to the Week 48 visit.
Evaluable biopsies were available at baseline and Week 48 for 11 subjects. The remaining 3 baseline biopsies were obtained but not suitable for histomorphometric analysis due to sample bone fragmentation, inadequate fixation, and/or poor labelling quality.

The mean age at enrolment was 40.1 years. Most subjects were female (57%), and most were white (64%). Mean (SD) serum phosphorus at baseline was 2.24 (0.396) mg/dL, below the normal range for adults (2.5-4.5 mg/dL). For further details, please refer to Table 16.

Exposure

As of the 30 Aug 2017 cut-off date, subjects had a median exposure of burosumab Q4W of 51.8 weeks (range, 43.9 to 75.7 weeks). The subject who withdrew consent received 12 doses of burosumab (last dose at Week 44) before withdrawal from the study.

Results

Histomorphometric Analyses (Primary and Secondary Endpoints)

The MAH has provided reference ranges for bone parameters healthy postmenopausal women (Recker et al. 1988):

- Osteoid volume as a percentage of total bone volume (OV/BV): 0.3% to 3.1%.
- Osteoid thickness (O.Th): 5.5-12 µm).
- Osteoid surface/bone surface (OS/BS): 7% to 25%

Due to mineralization defects, mineralization lag time (MLt) was not directly measurable at Baseline for 5 of the 11 subjects (45.5%) but was measurable in all but one Week 48 biopsy (10/11, 90.9%).

The results on the primary endpoint ((OV/BV) and the secondary histomorphometric endpoints are summarised in

Figure 31: Histomorphometric Parameters UX023-CL304

	Osteoid Volume/ Bone Volume (%)		Osteoid Thickness (µM)		Osteoid Surface/ Bone Surface (%)		Mineralization Lag Time (days) [a]	
	Baseline	Week 48	Baseline	Week 48	Baseline	Week 48	Baseline	Week 48
n	10	11	11	11	11	11	11	10
Mean (SD)	26.1 (12.4)	11.9 (6.6)	17.2 (4.1)	11.6 (3.1)	91.7 (3.4)	67.8 (13.7)	1539.8 (1587.1)	195.5 (77.7)
Median	24.1	9.20	16.2	11.4	92.0	73.0	1378.4	233.4
Min, Max	8.8, 49.9	3.2, 25.6	12.1, 24.7	7.2, 18.6	85.0, 97.0	34.0, 81.0	129.6, 4909.1	69.8, 281.9
Mean % Change from Baseline	--	-54.2%	--	-32.2%	--	-26.0%	--	-52.2%

The mean percent change from Baseline is based on Baseline of the subjects who had non-missing results at both Baseline and Week 48 visits. a using imputed results if reported results are missing

The percent change from baseline was statistically significant with p<0.0001 for OV/BV and O.Th and p=0.0002 for OS/BS.

Bone biopsies were also qualitatively analysed to assess the presence of osteomalacia. At Baseline, all subjects had osteomalacia as determined by evaluation of the iliac crest bone biopsy; nearly half of the subjects in the Primary Analysis Set (5/11, 45%) presented with severe osteomalacia. After 48 weeks of burosumab treatment, subsequent bone biopsy revealed severe osteomalacia in only 1 subject (9%), with mild osteomalacia in the remaining 10 subjects

Key Secondary Efficacy Endpoints: Proportion of Subjects Achieving Mean Serum Phosphorus Concentrations above the Lower Limit of Normal (LLN)

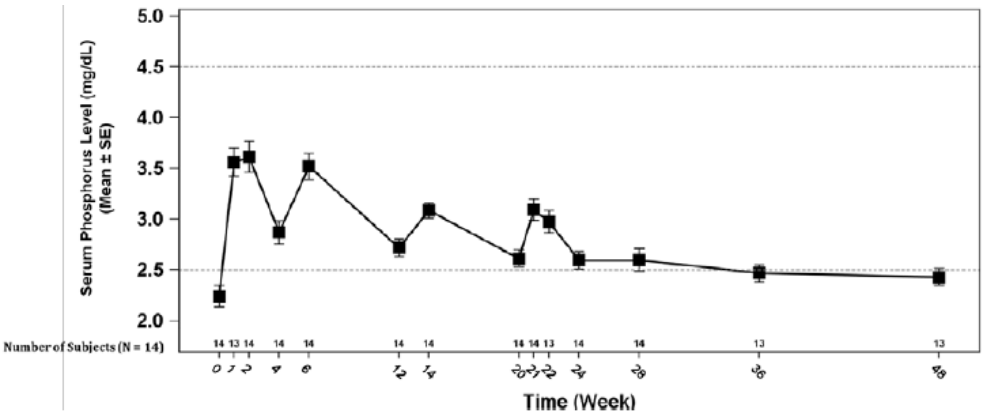
The key secondary endpoint of the study evaluated the proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal (LLN; 2.5 mg/dL [0.81 mmol/L]) at the mid-point of the dose interval (i.e., Weeks 2, 6, 14, and 22), as averaged across dose cycles between baseline and Week 24.

A total of 92.9% of subjects (13 of 14 subjects) achieved a mean serum phosphorus concentration above the LLN across the midpoints of dose intervals through Week 24 (95% CI: 68.5, 98.7; p-value < 0.0001)

Secondary Efficacy Endpoints: Other Analyses of Serum Phosphorus Concentrations

The serum phosphorus levels at the at the end of the dosing cycle (4 weeks after dosing) is shown in Figure 33.

Figure 32: Mean ± SE Serum Phosphorus Levels (mg/dL) (Full Analysis Set) in Study UX023-CL304.

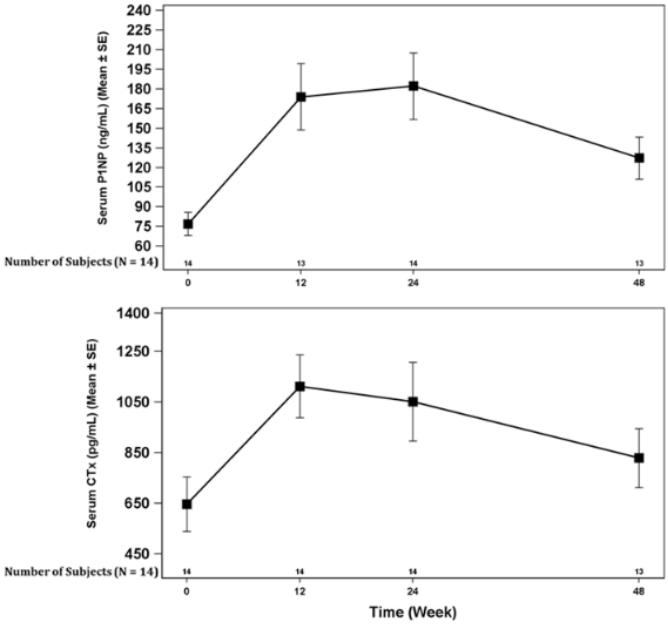


Dotted lines represent the upper limit of normal (4.5 mg/dL [1.45 mmol/L]) and the lower limit of normal (2.5 mg/dL [0.81 mmol/L])

Secondary Efficacy Endpoints: Bone Formation and Resorption Biomarkers

The effect on the bone formation marker P1NP (upper panel) and the bone resorption marker CTx (lower panel) are shown below.

Figure 33: Mean ± SE P1NP, and CTx Concentrations Through Week 48 (Full Analysis Set) UX023-CL304



Secondary endpoint: Changes from Baseline in MAR, MS/BS, BFR

Tetracycline irreversibly binds to hydroxyapatite at the mineralization front to allow for visualization and quantification of bone formation (Kulak et al. 2010).

Mineralization surface (MS/BS) represents the proportion of the bone surface that is active in mineralization at a specific time. At Baseline, mean (SD) MS/BS was 6.0% (4.76%). At Week 48, MS/BS trended towards increased mineralization, with a mean (SD) MS/BS 7.0% (3.65%), a mean (SD) change from Baseline of 1.3% (4.37%).

The mineral apposition rate (MAR), defined as the ratio of distance between two consecutive labels and time between the labelling midpoints (Dempster et al. 2013), was used to measure the rate of new bone deposition. At Baseline, mean (SD) MAR was 0.58 (0.448) µm/day. At Week 48, there was no meaningful change in MAR, with a mean (SD) of 0.62 (0.188) µm/day, a mean (SD) change from Baseline of 0.04 (0.506) µm/day.

The MAR is also used to derive the bone formation rate (BFR). After 48 weeks of burosumab treatment, there was no meaningful change in BFR/BS ratio, from a mean (SD) of 26.68 (19.480) µm3/µm2/year at Baseline to 17.17 (12.058) µm3/µm2/year at Week 48, a mean (SD) change from Baseline of -4.90 (27.356) µm3/µm2/year.

Exploratory Endpoint: Fracture healing

The baseline skeletal survey was read by a central radiologist who identified non-active (healed) fractures in 6 subjects (42.9%) and non-active pseudofractures in 5 subjects (35.7%). Although there were no active (unhealed) fractures reported for any subjects (0.0%), active pseudofractures were present in 4 subjects (28.6%). None of the active pseudofractures were worsened or unchanged following burosumab treatment, and there were no new findings (Table 35).

Table 33: Number of Active Pseudofractures Healed Over Time (Full Analysis Set)

	N=14
Number of Active Pseudofractures at Baseline	4
Week 12 grade – n (% baseline)	
Healed	2 (50.0)
Partially Healed	2 (50.0)
Week 24 grade – n (% baseline)	
Healed	2 (50.0)
Partially Healed	2 (50.0)
Week 36 grade – n (% baseline)	
Healed	2 (50.0)
Partially Healed	1 (25.0)
Missing	1 (25.0)
Week 48 grade – n (% baseline)	
Healed	3 (75.0)
Missing	1 (25.0)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of burosumab in adults with XLH was evaluated in two ongoing Phase 3 studies (UX023-CL303 and UX023-CL304), two Phase 1/2 adult studies (KRN23-INT-001 and KRN23-INT-002), and one long-term Phase 2b extension to the Phase 1/2 studies, Study UX023-CL203, for which a Week 48 analysis has been completed.
UX023-CL303 is the largest of the five studies and the only double-blind, controlled study in the adult clinical development program, and thus considered to be the main study.

Posology

The recommended posology for both adults and children is weight-based. For children, the approved starting dose is 0.4 mg/kg every second week (Q2W), the proposed maintenance dose 0.8 mg/kg Q2W and the maximal recommended weight-based dose is 2 mg/kg Q2W up to a total of 90 mg per administration.
The proposed starting dose in adolescents (0.8 mg/kg Q2W) is entirely based on PK/PD simulations.
In the proposed adult posology, the recommended starting dose is 1 mg/kg Q4W with a possibility to increase the dose up to a maximum of 90 mg per administration. This dosing was based on PK/PD-modelling and dose escalation in studies KRN23-INT-001/KRN23-INT-002. The same dose was used in studies UX023-CL303 and UX023-CL304. The mean administered dose in those studies ranged from 0.87 to 0.98 mg/kg.

Simulations from the PK/PD model showed that burosumab exposure estimates are greater following burosumab 0.8 mg/kg Q2W dosing than burosumab 1.0 mg/kg Q4W and differences in PK translates to relatively smaller changes from baseline of serum phosphorus due to saturation of the PK/PD mechanism. For the clinical endpoint of serum phosphorus levels, the predicted levels at Cmin, Cavg, and Cmax are all similar between the regimens. It should be noted that at all exposure measures, the 95th percentile of serum phosphorus predictions are greater following 0.8 mg/kg Q2W than those for burosumab 1.0 mg/kg Q4W. Given that events of hyperphosphataemia occurred following burosumab 1.0 mg/kg Q4W administration to adults in Study UX023-CL303, burosumab 0.8 mg/kg Q2W administration in adults may put this population at an increased risk for hyperphosphataemia. This potential for an increased risk of

hyperphosphataemia following burosumab 0.8 mg/kg Q2W suggests that this lower dose level, administered more frequently, would not be desirable to use in the adult population.

Study design UX023-CL303

The 24-week randomised, double-blind, controlled design of the treatment period in the main study UX023-CL303 is considered adequate, as is the open-label extension period. However, the choice of comparator (i.e., placebo) is acceptable as the practical feasibility of the alternative (conventional XLH treatment with oral phosphate and active vitamin-D analogues) could be questioned. Nevertheless, this implies that it is not possible in the current study to draw any conclusions on burosumab efficacy compared to conventional phosphate/D-vitamin treatment.

The key eligibility criteria for study UX023-CL303 are considered to reflect the intended target population and are therefore accepted.

The primary efficacy measure in study UX023-CL303 was the change in serum phosphorus levels. The change in serum phosphorus level could be considered a valid pharmacodynamic surrogate marker for the target molecule, FGF23. As such it is accepted. The relevance of increased serum phosphorus for clinical improvement is further discussed below.

The study includes several secondary and exploratory endpoints based on Patient reported outcome (PRO), including the key secondary endpoints. It is agreed that reports on the subjects' subjective perception of their symptoms are of high clinical relevance, however, such data needs to be interpreted with caution, especially in the open-label setting, where they are not considered reliable. Upon request, the MAH has justified the choice of the Brief Pain Inventory (BPI) Worst pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) stiffness and physical function domains as tools to evaluate the key secondary endpoints.

A sample size of 60 subjects per group was planned and since XLH is a rare condition, this sample size is reasonable. The sample size seems to have been based on the only key secondary endpoint that was identified originally, i.e. BPI Worst Pain. Later, when the study was already ongoing and the recruitment was probably completed, two additional key secondary endpoints were identified (see below under "Study conduct"). Nothing has been found regarding expected treatment difference or expected power to demonstrate superior efficacy on change from baseline week 24 in physical functioning (by WOMAC) or stiffness (by WOMAC), respectively. With the outcomes already at hand, this is however of lesser importance and by now a matter of assessment.

Study UX023-CL303 comprise a double-blind, placebo-controlled 24-week treatment Period, an open-label 24-week treatment continuation period during which subjects in the placebo group crossed over to treatment with burosumab, and an open-label 48-week treatment extension period. Focus for the assessment of the burosumab efficacy is the primary week 24 analysis (interim database lock on 23 March 2017). The SAP (version 1.0) was dated 28 November 2016 and the SAP version 2.0 was dated 31 January 2017, analysis details should thereby have been decided and defined prior to the performance of the primary analysis. In SAP version 2.0 a revision history is included describing the changes made and their rationale. This is appreciated.

The analysis of secondary endpoints was to be performed only if statistical significance ($p<0.05$) was reached in the analysis of the primary endpoint. This gatekeeping as well as the use of the Hochberg method for the three key secondary endpoints is agreed. The efficacy analysis was to include all randomised subjects who had received at least one dose of investigational product. This was achieved by all subjects and hence, the efficacy analysis was based on all randomised subjects. Both the analysis of the primary and key secondary endpoints, with one exception, were planned taking stratification factors into account. The exception was for the analysis of Worst Pain by BPI.

The primary Cochran-Mantel-Haenszel test and the GEE analyses used for the analyses of change from baseline for the key PRO endpoints could be acceptable albeit the latter could be criticised given the missing at random assumption and the applicant was further requested to better define the GEE model applied with a rationale for its appropriateness considering that the GEE technique is asymptotic, hence generally requiring large total sample sizes. Means and parametric approaches to statistical analysis are presented for many of the endpoints. These methods require assumptions around normality of underlying distributions within groups. The MAH was hence requested to confirm that the assumption of normality of the underlying data had been confirmed in all cases, particularly in relation to the primary and key secondary endpoints. Further, additional analyses were requested. The applicant used the Shapiro-Wilk test of normality to check the baseline data and the change from baseline data of key secondary PRO endpoints. The tests suggest that the change scores were non-normal for all measures (BPI Worse Pain Score, WOMAC Physical Function and WOMAC Stiffness) at 12 and 24 weeks for the burosumab group, and non-normal for WOMAC stiffness at 12 and 24 weeks for placebo. As requested, the MAH also reanalysed the key secondary endpoints using a repeated measures ANCOVA. However, Given the non-normality in the data further analysis for the normality of residuals and homogeneity of variance was presented to confirm the appropriateness of the ANCOVA method on these key secondary endpoints. This is accepted.
The working correlation/covariance structure used for the generalised estimating equations (GEEs) was compound symmetry, which assumes constant variance/covariance over time. The applicant was also to confirm whether this assumption is valid (particularly to week 24 but also to week 48) and to consider the use of an alternative covariance structure (i.e. unstructured) in a sensitivity analysis. As clarified with the MAH's response and the new analysis performed, the results at 24 weeks from using the Compound symmetry (CS) and Unstructured (UN) covariance structure were identical (to the third decimal place).

In the end, all subjects but one in the burosumab arm completed the double-blind 24-week treatment period. This does not necessarily imply that all patients had data for all measurement time-points; also, as clear from the presentation of outcomes, there were a few subjects excluded in the key secondary analyses and the applicant was requested to clarify. Further, a few additional analyses were requested whereof one of them was an analysis of Worst Pain (by BPI) that mirrored restrictions implied by actual randomisation.

Study conduct UX023-CL303

Due to a mistake in the IWRS, the actual randomisation stratification was based on the mean of the Brief pain index (BPI) *Average* Pain scores prior to baseline instead of on the mean of the 7 days of BPI *Worst* Pain diary scores prior to baseline visit, as specified in the study protocol.

The explanation for the randomisation error is stated to have been due to that the paper patient diary did not include questions 1 and 2 of the full BPI, BPI Q3 (Worst Pain) was hence labelled question 1 and BPI Q5 (Average Pain) was labelled question 3 of the patient diary. Therefore, IWRS was programmed to incorrectly stratify subjects based on the mean of the 7 daily diary labelled question 3. This sounds like a reasonable explanation and thereby there is no concern implied regarding the randomisation procedure and the stratification at randomisation per se.

Although it could be agreed that average pain and worst pain seem correlated, while balance was achieved for average pain at screening, there was an imbalance in pain intensity based on BPI worst pain between randomised arms, as BPI worst pain was >6.0 in 75% of the subjects in the burosumab versus 59% in the placebo arm. In addition: 'To assess the relationship of the stratification variables based on BPI Worst Pain and BPI Average Pain, the Pearson Correlation Coefficient will be obtained on the continuous variables of BPI Worst Pain and Average Pain.' This approach assumes the pain scores are normally distributed. As the scores may not be normally distributed and the sample size is not large, the MAH was requested to discuss whether use of a Spearman's correlation coefficient might have been more

appropriate in this instance. In reply, the MAH further assessed the relationship of Baseline BPI Worst Pain and Baseline BPI Average Pain with the Spearman's correlation coefficient with the final data from Study UX023-CL303. The correlation coefficients between these two pain scores were 0.82028 (Pearson, $p < 0.0001$) and 0.82332 (Spearman, $p < 0.0001$), respectively, both hence showing that the continuous variables of the two pain scores (BPI Worst Pain and Average Pain) at baseline were highly associated.

Overall, 40% of the study population were stratified as having a BPI ≤6/10 instead of >6/10, if the planned randomisation stratification had been used. This affected more subjects in the burosumab versus the placebo arm (46% vs 35%, respectively). However, a prespecified sensitivity analysis adjusting for the planned randomisation stratification based on BPI Worst Pain was consistent with the primary analysis based on the actual stratification, indicating that the erroneous stratification did not affect the outcome of the primary endpoint. It could however be expected to have had a greater impact on the key secondary analyses, as discussed below.

Originally, there was one key secondary endpoint (pain). Two "other" secondary endpoints, originally the last endpoints in a list of a number of secondary "other" endpoints, were identified and elevated as key secondary while the study was ongoing. This update was implemented in the study protocol with protocol amendment 3 i.e. only after the primary analysis database lock. In the study report for the week 24 analysis, amendment 3 is mentioned but not presented in the report. This is agreed. Instead, documentation that can support that all three key secondary analyses had been planned before the primary analysis data cut-off and the date for the data snapshot and unblinding of data, is found in the SAP (version 1.0, dated 28 November 2016). Upon request the MAH explained that the amendment in question took time to complete due to that several changes to the study protocol were discussed and that more data from another study (UX023-CL001) was awaited before finally deciding on key endpoints.

According to the MAH, the addition of two key secondary endpoints was made to reflect that for the purposes of the Week 24 primary statistical analysis, it was considered that the endpoint model that best characterized the clinical relevance of burosumab treatment on patient symptoms should analyse BPI Worst Pain, in conjunction with the WOMAC Stiffness and Physical Function domains as key secondary endpoints. This is not considered a sufficient justification for such an important alteration of key secondary endpoints at the end of the double-blind treatment period. The MAH was required to provide a scientific rationale for the amendment of two additional key secondary endpoints during the course of the study. The MAH has clarified that in discussing the study with the FDA, the FDA proposed to add BPI Worst pain as co-primary endpoint. However, the MAH decided to keep Serum phosphate as the single primary outcome and to instead assign BPI Worst pain a key secondary endpoint. The MAH explained their late action with a wish to await more data from another study (UX023-CL001) before finally deciding on key endpoints. After taking these results into consideration, the MAH decided that BPI Worst pain was not sufficient to address the spectrum of XLH symptomatology. In particular, according to the concept elicitation patient interviews, stiffness was the most prevalent and impactful XLH symptom. Therefore, the MAH decided to include WOMAC Stiffness and WOMAC Physical function as two supplementary key secondary endpoints in the study.

Major protocol deviations were reported more often in the burosumab treatment group (60% vs 46%). In addition, 7/68 (10%) of the burosumab treated subjects were partially unblinded at some time-point during the placebo-controlled treatment period versus none in the placebo arm, either accidentally or per protocol, due to hyperphosphataemia and sensitivity analyses for the primary endpoint and secondary endpoints, as well as for the 6MWT without the seven unblinded subjects and separately for the seven subjects. Regarding the five cases with unblinding of assigned treatment according to protocol due to a need of dose adjustments, the MAH has clarified that although the notation is "subject unblinded", it was only the investigator that was unblinded; the subject was still to be unaware of their assigned treatment. The protocol associated unblinding of fives subjects is therefore considered be of a lesser concern than initially thought.

Two additional subjects reported unblinding as major protocol deviation but according to the MAH, again only study personnel was unblinded to treatment. However, for one of these two subjects, a major protocol deviation of Unblinding described as "Patient had phosphorus level reported when completing local lab draw" was reported. This may indicate that the subject was actually informed. Notwithstanding, this is not expected to have affected the outcome.

In the provided plots, the results from the seven subjects with reported unblinding were distributed evenly within the remainder of the burosumab-treated group; however, there are two subjects that are among the extremes. It is unclear whether it is the same subjects irrespective of endpoint. As the MAH has clarified that in at least 6/7 events of unblinding, unblinding meant that the Investigator and site staff would have been exposed to the information and not the subjects, the issue is not further pursued.
The sensitivity analyses performed implies, as could be expected, decreased differences between the two randomised arms. For BPI Worst pain and WOMAC Physical Function that did not reach statistical significance in the primary analysis, there is no change regarding what conclusions that can be drawn. For WOMAC Stiffness the difference between treatment arms was no longer statistically significant. Taking the clarifications regarding the nature of unblinding into account, the primary conclusion is still considered valid.

Stratification by region was not specified in the protocol but is stated to have been conducted for operational and logistic considerations. The justification for why region was used for stratification is acceptable; the failure of describing this in the study protocol could be considered worrying regarding study conduct. An update of the study protocol to clarify that randomisation was stratified not only by baseline pain intensity, but also by region (North America/European Union, Japan, and South Korea) was only made long after recruitment was completed, i.e. within protocol amendment 3 after the interim database lock (amendment 3 was dated 31 March 2017, the Interim Database Lock occurred 23 March 2017). The balance achieved between the treatment arms support that randomisation was stratified also for region. However, the numbers outside US/Europe were very small (only 18 in total) limiting generalisability.

In a limited study population, double stratifications inevitably lead to some imbalances between the treatment arms for other baseline parameters. Baseline serum phosphorus, which is assessed in the primary endpoint, was comparable between the treatment arms: 1.92 mg/dL [0.62 mmol/L] in the placebo arm and 2.03 mg/dL [0.66 mmol/L] in the burosumab arm. The mean age was somewhat higher in the burosumab arm compared to placebo (41.3 vs 38.6 years, respectively). This is not expected to affect the outcome of the study per se. However, there were more subjects in the oldest age range (> 50-65 years) in the burosumab group vs placebo (16 vs 10). An older patient population with a longer disease duration may influence the results, particularly in relation to the secondary and exploratory endpoints. Upon request, the MAH has conducted subgroup analyses demonstrating that no significant interaction was identified for the primary endpoint, nor for the key secondary endpoints of WOMAC Physical Function, WOMAC Stiffness and BPI Pain. Further, the small non-statistically significant difference in the number of patients aged >50 years between the placebo and burosumab groups is unlikely to have affected the results.

Due to the erroneous stratification by baseline pain, there was an imbalance in pain intensity between the treatment arms, as BPI worst pain was >6.0 in 75% of the subjects in the burosumab versus 59% in the placebo arm. This may have impact in the Patient reported outcomes (PROs). Both osteoarthritis and nephrocalcinosis were reported more often at baseline in the treatment arm (69% vs 58% respectively for osteoarthritis and 16% vs 8% for nephrocalcinosis), as were Musculoskeletal and connective tissue disorders (44% vs 36%) and General disorders and administration site conditions (mainly pain, fatigue and pyrexia) (21% vs 14%). These are symptoms that may be associated with XLH. Also, even though the use of pain medication per se was balanced between the treatment arms (burosumab 69%, placebo 67%), use of opioids was more common in the burosumab arm, 25% vs 20% in the placebo arm.

Furthermore, use of the "other" pain medications was imbalanced between treatment groups, being reported by 10% of subjects in the burosumab group versus 1.5% of subjects in the placebo group. Taken together, this may implicate that the treatment arms were not fully balanced regarding baseline pain and XLH manifestations. The MAH was asked to comment on the any potential impact of this imbalance on the outcome of the study, particularly with respect to the key secondary objectives. In response, the MAH provided interaction analyses. The MAH argues that the unbalance has had negligible impact on the study outcome. According to the MAH, one statistically significant interaction was detected, between presence of nephrocalcinosis at baseline and BPI Worst Pain (p= 0.0475). The observed interaction between the presence of baseline nephrocalcinosis and BPI Worst pain is difficult to interpret as nephrocalcinosis is normally asymptomatic. The value of interaction testing is limited in such small population as the power for detection of interactions is considered too low.
The Applicant has provided Forest plots displaying subgroup analysis for five baseline parameters not fully balanced, i.e. use of pain medication, use of opioid pain medication, baseline presence of osteoarthritis and baseline presence of nephrocalcinosis, with regard to the three key secondary endpoints as requested. None of the subgroups showed a consistent additional benefit in favour of burosumab across these key secondary endpoints, above that seen in the All Subjects group. Although statistical significance was not shown for most subgroups, the point estimate favours burosumab in all subgroups for the three key secondary endpoints.

The data cut-off date for the primary week 24 analysis was 22 December 2016. After the interim database lock and subsequent unblinding of data for the primary week 24 analysis on 23 March 2017, the database was unlocked and relocked twice, in September 2017 and in October 2017. According to the applicant, each unlock and relock followed standard operating procedures. The data changes at the site level requiring the unlocks were: (1) WOMAC Stiffness; (2) six-minute walk test (6MWT) baseline distance; and (3) several AEs that investigators had updated or added. This implied that e.g. WOMAC Stiffness, i.e. one of the three proposed key secondary endpoints, was re-analysed and currently it is the results from this re-analysis that has been presented. This was not agreed and the MAH has presented arguments for why the corrected analysis is considered valid. However, despite that the correction of data may have been with all the best operating procedures in place, it was based on what may have been a minor mistake, and for the endpoint based on WOMAC Stiffness, concerned one data point alone. This is a question of scientific integrity and validity that applies in general, irrespective of the nature of correction. Hence, the only formally valid outcome is the one based on the data collected and cleaned before unblinding (see below).

Study conduct UX023-CL304

Originally, the four bone mineralisation parameters Osteoid volume as a percentage of total bone volume (OV/BV), Osteoid thickness (O.Th), Osteoid surface/bone surface (OS/BS) and Mineralization lag time (MLt) were all listed as primary endpoints, but in protocol amendment 2, dated 07 October 2016, this was narrowed to leave OV/BV as the single primary efficacy endpoint. The other histomorphometric parameters were specified as secondary endpoints. This was done during the course of the study (First subject signed informed consent, 23 December 2015), but before the data cut-off date for this report, 30 August 2017.
The MAH has clarified that the primary analysis was narrowed to focus on osteoid volume, as all four parameters as the primary endpoints would have made the proper evaluation and interpretation of study results more complex without considering the multiplicity. The four parameters are not fully independent of each other, as the osteoid volume (OV) is the product of osteoid thickness (OTh) and osteoid surface (OS), which can support the use of osteoid volume/bone volume (OV/BV) only as primary endpoint.

Efficacy data and additional analyses

Study populations

The mean age across the studies ranged from 40 to 50 years. In all studies, most subjects (57-70%) were women and most subjects (64-96%) were white.

In all studies except UX023-CL304, baseline serum phosphorus ranged from 1.85-1.98 mg/dL [0.60-0.64 mmol/L] (normal range 2.5-4.5 mg/dL [0.81-1.45 mmol/L]), whereas in UX023-CL304, baseline serum phosphorus was 2.24 mg/dL [0.72 mmol/L].
In the other studies in adult XLH patients, subjects receiving concomitant treatment with phosphate supplementation and/or D-vitamin analogues within 10-21 days prior to screening. As opposed to this, in study UX023-CL304, the use of phosphate supplementation and/or D-vitamin analogues were not allowed within two years prior to screening. The small difference in mean baseline serum phosphorus may indicate that this difference in eligibility criteria resulted in a slightly different study population in UX023-CL304 compared to the other studies.

With the exception of Study KRN23-INT-001, where 5/30 subjects (17%) discontinued treatment, 90-100% of the subjects in the clinical studies completed the study treatment.

Results

Serum phosphate (primary and secondary endpoints)

Study UX023-CL303 met its primary endpoint as a considerably larger proportion of the subjects in the burosumab versus the placebo treatment arm achieved mean serum phosphorus levels above the lower level of normal at the midpoint of the dose interval (94% vs 8%, respectively; $p<0.0001$).

A pre-specified sensitivity analysis of the primary endpoint was performed to assess the impact of the stratification misclassification using BPI Average Pain rather than the planned BPI Worst Pain score for randomisation. This analysis produced identical results as those of the primary analysis.

Sensitivity analyses and several subgroup analyses were all consistent with the primary analysis with one exception. For the subgroup of subjects from South Korea, a significant difference between treatment groups was not observed. However, this subgroup included only four subjects in the burosumab group and three subjects in the placebo group, precluding relevant conclusions.

In the burosumab arm, baseline mean serum phosphate was 2.03 mg/dL [0.66 mmol/L] and serum phosphorus across the midpoints of dose cycles during the placebo-controlled period through Week 24 was 3.24 mg/dL [1.05 mmol/L], levelling out to 3.02 mg/dL [0.98 mmol/L] Week 24-48. The corresponding vales for the placebo arm was 1.92 mg/dL [0.62 mmol/L] at baseline and 2.08 mg/dL [0.67 mmol/L] across the midpoints of dose cycles through Week 24.
Mean serum phosphorus at Week 24 (trough level) was 2.53 mg/dL [0.82 mmol/L] in the burosumab arm and 2.07 mg/dL [0.67 mmol/L] in the placebo arm. The corresponding number at Week 48 was 2.47 mg/dL [0.80 mmol/L] for both treatment arms. Thus, the increase in trough phosphate level seems to be sustained up to 48 weeks.

Serum phosphate was a primary or secondary endpoint in the open-label studies in the adult clinical development program. The results from these studies support the result from main study UX023-CL303.

The increase in serum phosphorus concentration with burosumab treatment in adults is considered solid and convincing. This is a clear indication that the effect of burosumab on FGF23 function in adults is consistent with the effect in the paediatric population. Even though serum phosphate could be seen as a surrogate pharmacodynamic marker for clinical effect, chronic hypophosphataemia is a major contributor to the pathophysiology of the disease. Low serum phosphate hampers normal bone calcification and bone

remodelling, which in turn leads to rickets symptoms, i.e. impaired skeleton development with short stature, bowing and bone deformity in children and to fractures, pseudofractures and enthesopathy in adults. Secondary to this, osteoarthritis and joint destruction may develop due to skeletal malformation and misalignment of joints, all with a major impact on the patients' quality of life. In severe hypophosphataemia, the low serum phosphate concentration per se may be also symptomatic. Some of these XLH manifestations are considered irreversible while others, e.g. bone mineralisation, are deemed modifiable with treatment. It is considered reasonable to assume that normalisation of serum phosphate may be beneficial also in the adult population.

Other pharmacodynamic endpoints

The high serum levels of FGF23 associated with XLH inhibits phosphate reabsorption in the kidneys, as determined by renal tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR). As expected from the mechanism of action, TmP/GFR increased with burosumab treatment in all studies. In UX023-CL303, the difference between the treatment arms was significant Week 24.

Vitamin-D is suppressed by FGF-23. This is at least a part of the explanation to why Serum Vitamin-D (i.e., 1,25(OH)2D) is low in XLH-patients in spite of their hypophosphataemia, which is normally a strong stimulator of active Vitamin-D. Decreasing FGF23 levels by burosumab treatment led to a rapid increase 1,25(OH)2D in all studies, which was also expected. In UX023-CL303, the difference between the treatment arms was significant Week 22 (1,25(OH)2D was not measured at Week 24)
This increase was not sustained throughout the study durations. It is hypothesised by the MAH that this likely represents normal feedback regulation as phosphate-calcium homeostasis improves with burosumab therapy.

Patient reported outcome scales (secondary endpoints).

Patient reported outcome scales (PRO) were secondary endpoints in UX023-CL303 and secondary endpoints in all studies. The reliability of subjective reports of perceived symptoms in an open-label setting is questioned. This is exemplified by the WOMAC Stiffness and WOMAC Physical Function scores in study UX023-CL303, where improvement in LS mean from baseline in the burosumab treatment arm levelled out between Week 12 and Week 24 but increased again between Week 24 and Week 48, implicating that the open-label design may indeed have affected the outcome. Therefore, only PRO data from the placebo-controlled, double-blind period of UX023-CL303 are discussed below.

The Brief Pain Inventory (BPI) scales are 10-point scales from 0 (no pain) to 10 (as bad as you can imagine). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scales ranges from 0 (best health state) to 100 (worst).

As discussed above, the BPI Worst Pain score at week 24 was the only originally prespecified key secondary endpoint that was tested at 0.05 significance level. The mean worst pain decreased in the placebo group from 6.5 to 6.1 and from 6.8 to 5.8 in the burosumab group. The difference was not statistically significant.

WOMAC Stiffness score and WOMAC Physical Function score were identified as key secondary efficacy endpoints in addition to BPI Worst Pain score during the course of the study. Both scales shoved improvements in the burosumab arm compared to placebo. In the burosumab arm, WOMAC Physical Function score decreased from 51 to 43 points between baseline and Week 24 compared to 44 to 43 in the placebo arm. The baseline scores were not balanced between the treatment arms; in fact, the difference between the baseline score was similar to the difference between baseline and Week 24 score in the burosumab arm. The corresponding numbers for WOMAC Stiffness score was 65 to 54 in the burosumab arm and 61 to 60 in the placebo arm. In this analysis, the baseline scores were better balanced. Applying the Hochberg adjustment for multiple testing for the three endpoints, the difference between the treatment arms in WOMAC Stiffness score at Week 24 was significant at the $p<0.0167$ level.

Upon request, the MAH has provided information on what could be considered minimal clinical important difference (MCID) for the key secondary endpoints. According to the MAH, the MCID for adults with XLH are 1.72 for the BPI-SF Worst Pain score, 9.3 for the WOMAC Physical Function score, and 10.0 for the WOMAC Stiffness score. For WOMAC Stiffness, mean improvement corresponding to MCID was reached by approximately Week 36 and for WOMAC Physical function beyond Week 96, whereas the mean improvements did not reach MCID for BPI Worst pain during the course of the study.

As stated by the applicant, model-based estimates for WOMAC Stiffness, 6MWT, and fractures were reanalysed for the placebo-controlled treatment period because additional or corrected data were provided for these endpoints after the interim database lock for the primary analysis. Presented above is the post-hoc "corrected" analysis of WOMAC Stiffness. In the original analysis presented in the Week 24 analysis CSR, the LS mean (SE) difference between treatment groups (burosumab-placebo) in the change from baseline to Week 24 was -8.1 (3.24) (p=0.0122); to be compared with the outcome from the reanalysis -8.3 (3.25) (p=0.0106). The difference between the treatment arms was statistically significant irrespective of analysis and the difference in the point estimates minor. Whenever applicable, it should however be the original analysis that is presented e.g. in section 5.1 of the SmPC.

As reported by the applicant, all subjects but one continued in the study through week 24. To be included in the analysis of the key PRO endpoints, subjects were required to have a baseline and at least one post-baseline assessment. In the analyses, data from one (placebo) or, one or two subjects (burosumab) have been excluded. Although small numbers, the applicant was requested to clarify and, in addition, clarify whether there were any patients that were included in the analyses that lacked measurements at week 24. In response, the MAH has made clear that all subjects had available baseline and week 12 data, albeit three subjects, one in the placebo arm and two in the burosumab arm, had missing or partially missing data at Week 24 and also that they, contrary to the assessor's interpretation, were included in the Week 24 analysis of BPI Worst Pain, WOMAC Stiffness and WOMAC Physical Function. Sensitivity analyses have been presented using LOCF, BOCF and mBOCF imputation methods respectively. Irrespective of method used, outcomes were consistent with those from the primary analysis. All three imputation methods can however be criticised. The MAH replied that other approaches were not considered in the Study UX023-CL303 SAP, primarily because it was anticipated that there would be very few missing data. Given analysis results and provided the number of subjects with missing data remains at three, no new sensitivity analyses are considered needed.

Sensitivity analyses of the (key) secondary endpoints were performed to assess the impact of randomisation stratification by average pain (BPI Q5) rather than the planned stratification by worst pain (BPI Q3)//which used the planned randomisation stratification factor based on BPI Worst Pain score instead of the actual randomisation stratification factor based on BPI Average Pain score in the GEE model. These are endorsed for sensitivity purpose.

For change from baseline to Week 24 in BPI Worst Pain score, the sensitivity analysis adjusted for the baseline BPI Average Pain score instead of the baseline BPI Worst pain score in the GEE model. The outcome was similar to the outcome of the primary analysis. In change from baseline analyses, the baseline value should be included as a covariate, i.e. baseline BPI Worst pain score should be included in the analysis of change from baseline to Week 24 in BPI Worst Pain score. Instead, considered lacking was an analysis reflecting the restriction on the randomisation implied by the stratification using a model that also included the baseline BPI worst pain score as a covariate. Two analyses were requested; one adjusting for the actual stratification factor (average pain) and one adjusting for the planned stratification factor (worst pain). These have been provided, showing only minor differences compared with the initially presented primary analysis.

The secondary endpoints in UX023-CL303 also included BPI Pain Severity, BPI Pain interference, Brief Fatigue Inventory (BFI; range 1-10) Worst Fatigue, and BFI Global Fatigue. There was a trend towards a

favourable effect of burosumab in BPI Pain Severity score; however, no difference between the treatment arms was seen in BPI Pain interference, BFI Worst Fatigue, and BFI Global Fatigue.

Patient's Global Impression of Improvement (PGI-I) was included as an exploratory endpoint in UX023-CL303. In this assessment, the subjects first scored their perception of disease severity on a scale from 1 (normal) to 4 (severe) according to the Patient Global Impression of Severity (PGI-S) instrument at baseline, thereafter, at week 24, the perception of improvement with treatment over time was scored on a scale from 1 (very much better) to 7 (very much worse) according to the PGI-I. No meaningful difference between the treatment arms in PGI-I was seen at Week 24.

In summary, the results from the PRO endpoints are not fully concordant, with a trend towards a positive impact of burosumab on BPI Worst Pain, WOMAC Stiffness score (significant if applying the Hochberg adjustment for multiple testing), WOMAC Physical Function and BPI Pain Severity but with no meaningful difference between the treatment arms in BPI Pain interference, BFI Worst Fatigue, BFI Global Fatigue and PGI-I. Notwithstanding, while the quantitative effect of burosumab on PROs is considered modest, patients' experiences of symptom and activity improvement, as reported in patient interviews and feedback, support the view that the effects are meaningful to patients. The totality of these data and the consistency of effect among the assessments demonstrate that, despite the long-term complications and symptoms experienced by adults with XLH, burosumab improves symptoms and function that are clinically meaningful to patients.

Bone related endpoints

The primary objective in study UX023-CL304 was to establish the effect of burosumab treatment on improvement in XLH-associated osteomalacia (defective bone mineralisation) as determined by ration between osteoid (unmineralized bone) volume and total bone volume (OV/BV) by iliac bone biopsies. OV/BV is elevated in osteomalacia.
The study met its primary endpoint as the increased OV/BV ratio decreased by 54% from baseline to Week 48 ($P<0.0001$).

This is supported by statistically significant reductions also in osteoid thickness (OTh) and in ratio of osteoid surface to total bone surface (OS/BS). In comparison to reference ranges for histomorphometric bone parameters in healthy postmenopausal women (Recker et al. 1988), none of the parameters were fully normalised. At Baseline, all subjects had osteomalacia as determined by evaluation of the iliac crest bone biopsy; nearly half of the subjects in the Primary Analysis Set (5/11, 45%) presented with severe osteomalacia. The MAH has clarified that after 48 weeks of burosumab treatment, subsequent bone biopsy revealed severe osteomalacia in one subject (9%), with mild osteomalacia in the remaining 10 subjects. This suggests that the normalisation of bone structure is slow.
Other secondary endpoints in this study were mineralization lag time (MLt), the proportion of the bone surface that is active in mineralization at a specific time (MS/BS) and the bone formation rate per bone surface (BFR/BS). Due to the large number of imputed values, the results on mineralization lag time (MLt) are not considered fully robust.
Notable, at Week 48, the bone formation rate per bone surface (BFR/BS) was actually lower than at baseline (mean [SD] change from Baseline of -4.90 [27.356] µm3/µm2/year); however, the large SD precludes any firm conclusions.

Taken together, the data from Study UX023-CL304 support a positive effect of burosumab on bone mineralisation.

This is further supported by the effect on pharmacodynamic bone markers. In all adult studies, burosumab effect on the bone formation marker P1NP and the bone resorption marker CTx was either a primary pharmacodynamic endpoint (UX023-CL203) or a secondary pharmacodynamic/efficacy endpoint (the other studies). For both markers, a marked increase was seen on burosumab treatment, reaching

maximum after 12-24 weeks of treatment, after which a decrease towards baseline is seen; however, the levels remaining above baseline at Week 48. In their response document, the MAH has provided data on the bone formation marker P1NP and the bone degradation marker CTx up to Week 96 in Study UX023-CL303 and UX023-CL304. In both studies, serum concentration of P1NP and CTx continued decreasing towards, but not reaching, baseline values at Week 96. In Study UX023-CL303, the decrease in serum concentrations for both markers were very similar in both treatment arms however with a delay of 24 weeks in the placebo→burosumab group. The increase in P1NP seemed to be more pronounced and the decrease slower than that of CTx in both studies, suggesting a positive remodelling balance with a net increase in bone formation. The slow normalisation of bone structure as discussed above may serve as an explanation to why the bone markers P1NP and CTx remain elevated beyond Week 96.

Fracture/pseudofracture healing and enthesopathy

Fracture/ pseudofracture healing were assessed in studies, UX023-CL303, UX023-CL203 and UX023-CL304.

In study UX023-CL303, healing of active fractures and pseudofractures detected by x-ray at baseline to the end of the study was an exploratory endpoint, which hampers the impact of the data.
To minimise the risk of bias in reviewing-rays, the MAH contracted Biomedical Systems, Inc. (BMS) to provide an independent review of site-acquired x-ray data. One independent reviewer was to review the baseline skeletal survey x-rays and indicate if there are active or non-active bone fractures and pseudo-fractures and their locations. Two different independent reviewers assessed the targeted x-ray time point images, comparing the current time point image with the image from the baseline time point or the time point the fracture was initially identified. This approach is considered acceptable.

In the burosumab treatment arm more active fractures were healed (7/14 [50%]) or partially healed (3/14 [21%]) at Week 24 compared to placebo (0% and 6/13 [46%], respectively). The corresponding numbers for active pseudofractures were 21/51 [41%] healed and 13/51 [26%] partially healed in the burosumab arm and 7/78 [9%] and 22/78 [28%], respectively, in the placebo arm.
The numbers indicate a difference in fracture/pseudofracture healing in favour of burosumab. However, additional new fractures/pseudofractures occurred in both arms by the week 24; 8 in the placebo arm and 6 in the burosumab arm. As discussed above, bone structure was not completely normalised at Week 48 in bone biopsies in Study UX023-CL304, indicating that normalisation of the bone may take months or even years. This could contribute to a continued incidence of new fractures despite burosumab treatment. This may be further supported by the fact that six new fractures were reported in the burosumab arm Week 0-24 compared to one fracture Week 24-36 and none Week 36-48.

No comparison in fracture healing between the treatment arms was planned. In a post hoc analysis using a hierarchical generalised linear mixed proportional odds model showed an odds ratio between burosumab vs placebo for fracture healing of 16.8 (95% CI 4.9, 57.0; $p<0.0001$).

Data on fracture healing from study UX023-203 will be provided separately according to the MAH. It is not specified whether this will be done within this procedure or in the final study report.

In study UX023-CL304, four active pseudofractures and no active fractures were reported in 14 subjects at baseline. At Week 48, three of the pseudofractures were fully healed and no information was available in the remaining case. Due to the low number of events, no conclusions are possible, especially in the absence of healing time for pseudofractures in adult XLH subjects without treatment. The absence of new events during the 48-week period is however acknowledged.

No positive burosumab effect on enthesopathy burden was seen at Week 24. In fact, a numerically, but not statistically, better effect was seen in the placebo treatment arm. However, the MAH's note that due to inclusion of this analysis in an amendment during the course of the study, only approximately 10-12 subjects in each treatment arm had Week 24 measurement. Notwithstanding, the LS mean change from

Baseline to Week 48 was -0.53 cm in the burosumab→burosumab group and -0.12 cm in the placebo→burosumab group. Thus, there was no meaningful change from Baseline at Week 48 for total calcaneal enthesopathy burden. Additional data provided as response to the first List of questions indicate that no positive effect on enthesopathy was seen beyond Week 48 either in Study UX023-CL303. The MAH has clarified that enthesopathy is not considered a modifiable manifestation of XLH.

The MAH points out that adult XLH patients have pain from many sources (e.g. skeletal deformity, osteomalacia, osteoarthritis, pseudofractures and fractures, enthesopathy), not all aspects of which may resolve with burosumab treatment due to their cause or chronicity. It is acknowledged that these subjects have lived all their lives with the cumulative effects of abnormal bone mineralization and carry a substantial, unresolved burden of disease. In the context of chronic osteomalacia, full recovery of bone health may require longer burosumab treatment. A range of studies are planned aimed at collecting longer term data on bone health in burosumab treated patients. These include two extension studies (BUR-02 and KRN23-004) to the phase 3 studies (UX023-CL303 and UX023-CL304), UX023-CL401 which is a 10-year DMP, the European registry (2018-16-EU-BUR) which will run for 10 years and an Asian observational study (Sunflower) of 5-year duration. Relevant safety reports and study progress reports will be provided in routine PSURs.

Mobility test

Six-minute walking test (6MWT) and "timed up and go"-test (TUG) were exploratory endpoints in UX023-CL303.

6MWT showed an improved mean walking distance of 14.8m at Week 24 and of 30.5m at Week 48 from mean baseline walking distance (357 m) in the burosumab arm. In the placebo treatment arm, the mean walking distance decreased with 5 m through Week 24. The recorded difference between the groups is deemed clinically relevant.

TUG was added as an exploratory endpoint approximately 9 months after enrolment of the first subject No baseline values are recorded and only nine Week 24-recordings of TUG exist in study U023-CL303. Therefore, no meaningful analysis of this endpoint is deemed possible.

In Study UX023-CL302, a strong positive trend on 6 MWT and a statistically significant effect on TUG was seen with burosumab treatment.

Assessment of paediatric data on clinical efficacy

Crysvita has a conditional marketing authorisation for treatment of children with XLH from the age of one year and adolescents with growing skeletons. No children were included in the studies forming the adult clinical development program assessed in this report.

Adolescents with closed epiphyseal growth plates have not been included in any clinical studies, neither in the paediatric nor the adult development program. However, the applicant states that in the primary paediatric Study UX023-CL201, supporting the current indication, that there were 11 adolescent subjects included identified as having closed growth plates during the study. This is further discussed in the clinical safety section.

The proposed posology for this population is based on PK/PD modelling. This is further discussed in the pharmacokinetic section.

It is considered reasonable that the effect of burosumab could be extrapolated from the adult population given the same exposure.

2.4.4. Conclusions on the clinical efficacy

The increase in serum phosphorus concentration with burosumab treatment in adults is considered solid and convincing. This is a clear indication that the effect of burosumab on FGF23 function in adults is consistent with the effect in the paediatric population. Even though serum phosphate could be seen as a surrogate pharmacodynamic marker for clinical effect, chronic hypophosphataemia is a major contributor to the pathophysiology of the disease. It is anticipated that normalisation of serum phosphate may have a beneficial effect on modifiable XLH manifestations, e.g. improved bone calcification, and possibly also decrease the deterioration rate of irreversible XLH damages. In addition, normalisation of serum phosphate should have a direct positive effect on symptoms from low serum phosphate per se, e.g. muscle weakness and fatigue. It is therefore agreed with the MAH, that the increase in serum phosphorus concentration with burosumab treatment in adults could be considered clinically relevant.

While the quantitative effect of burosumab on PROs is considered modest, patients' experiences of symptom and activity improvement, as reported in patient interviews and feedback, support the view that the effects are meaningful to patients. Limited data on fracture healing, bone mineralisation and bone markers also pose a support for a positive effect of burosumab also in adults with XLH.

Some issues related to study conduct were identified, e.g. alterations of the primary and key secondary endpoints, respectively, in studies UX023-CL304 and UX023-CL303 during the course of the study, failure to update the study protocol with this information in due time, erroneous stratification leading to some imbalance in baseline parameters etc. These issues were adequately addressed by the MAH during the procedure.

The statistical methodology used for the analyses of change from baseline for the key PRO endpoints has been questioned. The MAH was requested to confirm that the assumption of normality of the underlying data had been confirmed in all cases, particularly in relation to the primary and key secondary endpoints. Further, additional analyses were requested. The applicant used the Shapiro-Wilk test of normality to check the baseline data and the change from baseline data of key secondary PRO endpoints. The tests suggest that the change scores were non-normal for all measures. As requested, the MAH also reanalysed the key secondary endpoints using a repeated measures ANCOVA. Further analysis for the normality of residuals and homogeneity of variance was presented to confirm the appropriateness of the ANCOVA method on these key secondary endpoints. This is accepted.

Taken together, a positive effect of burosumab is considered shown also in the adult and adolescent populations.

2.5. Clinical safety

Introduction

The currently approved indication in paediatric patients (i.e. treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons) was primarily based on data from completed Study UX023-CL201 and ongoing Study UX023-CL205.

Study UX023-CL201 was a Phase 2, randomised, open-label study of 52 children between the ages of 5 to 12 years with XLH, and Study UX023-CL205 is a Phase 2, open-label study of 13 children between the ages 1 to 4 years with XLH. In addition, data from ongoing Study UX023-CL301 (a randomised, Phase 3, open-label in 61 children between 1 and 12 years) have been provided in order to increase the recommended starting dose in children to 0.8 mg/kg (variation II/04).

The Summary of clinical safety (SCS) for adult XLH is based primarily on data from ongoing Phase 3 Studies UX023-CL303 (double-blind, placebo-controlled) and UX023-CL304 (open-label), supported by data from ongoing open-label Phase 2 Study UX023-CL203 and 2 completed open-label Phase 1/2 studies (KRN23-INT-001 and KRN23-INT-002) (Table 36).

*Table 34: Dataset Included in Clinical Summary of Safety of **Adult XLH***

Study ID	Number of Burosumab Subjects	Study Type	Study Status	Data Cutoff Date [a]
UX023-CL303	134 [b]	Repeat dose, double-blind, placebo-controlled	Ongoing	08 Jun 2017 Available data: Week 48
UX023-CL203	20	Repeat dose, open-label	Ongoing (enrollment is closed)	08 Jun 2017 Available data: Week 48
UX023-CL304	14	Repeat dose, open-label	Ongoing	30 Aug 2017 Available data: Week 48
KRN23- INT-001	28	Repeat dose, open-label	Completed LPLV: 10 Apr 2013	Minimum treatment: 4 weeks
KRN23- INT-002	22	Repeat dose, open-label	Completed LPLV: 10 Apr 2013	Minimum treatment: 4 weeks

Note: Study KRN23-INT-002 was an extension study of subjects who participated in Study KRN23-INT-001 and met protocol criteria. Subjects in KRN23-US-02, KRN23-INT-001, and KRN23-INT-002 who met protocol criteria could participate in Study UX023-CL203.
a: The cut-off date for SAE narratives reported in this document was 18 Feb 2019.
b: At Week 24, subjects on placebo crossed over to receive burosumab.

LPLV = last patient last visit; SAE = serious adverse event; XLH = X-linked hypophosphataemia.

The adult safety assessment focuses on Study UX023-CL303, as it provides a placebo-controlled assessment of safety, comprises 76% (134/176) of the adult safety dataset, and largely represents the overall adult XLH subject population. Adult subjects in Study UX023-CL303 may have participated in up to 2 burosumab studies; a total of 7 subjects in Study UX023-CL303 had previously participated in Studies KRN23-INT-001 (1 subject), KRN23-US-02 (2 subjects) and KRN23-001 (4 subjects).

Patient exposure

Details of repeat-dose exposure to burosumab in adult XLH subjects are summarised in Table 37.

*Table 35: Exposure to Burosumab: Repeat-dose Studies in **Adult XLH***

	UX023-CL303			UX023-CL304	UX023-CL203	KRN23-INT-001/002 [b]	
	Double-blind Period (Week 0-24)		Total				Overall
	Placebo (N = 66)	Burosumab (N = 68)	Burosumab (N = 134) [a]	Burosumab (N = 14)	Burosumab (N = 20)	Burosumab (N = 28)	Burosumab [c] (N = 176)
Cumulative exposure (subject years)	30.34	31.30	123.42	13.90	40.88	26.81	205.00
Duration of exposure (weeks)							
Mean (SD)	23.99 (0.301)	24.02 (0.312)	48.06 (15.074)	51.80 (8.254)	106.65 (11.519)	49.96 (21.941)	60.78 (38.946)
Median	24.00	24.00	51.36	49.93	108.00	63.79	51.93
Q1, Q3	23.86, 24.14	23.86, 24.14	32.57, 60.14	47.71, 52.71	101.93, 115.93	28.21, 64.21	36.21, 64.21
Min, Max	23.0, 24.4	23.3, 25.3	23.6, 76.0	43.9, 75.7	73.1, 120.1	4.0, 64.7	12.0, 184.1
Duration of exposure in category (weeks) – n (%)							
≥1 day to <12 weeks	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.6%)	0 (0%)
≥12 to <24 weeks	24 (36.4%)	25 (36.8%)	2 (1.5%)	0 (0%)	0 (0%)	6 (21.4%)	5 (2.8%)
≥24 to <48 weeks	42 (63.6%)	43 (63.2%)	60 (44.8%)	4 (28.6%)	0 (0%)	2 (7.1%)	65 (36.9%)
≥48 to <72 weeks	0 (0%)	0 (0%)	62 (46.3%)	9 (64.3%)	0 (0%)	19 (67.9%)	75 (42.6%)
≥72 weeks	0 (0%)	0 (0%)	10 (7.5%)	1 (7.1%)	20 (100.0%)	0 (0%)	31 (17.6%)
Total burosumab dose (mg)							
Mean (SD)	0.00 (0.000)	403.88 (99.220)	799.99 (321.970)	864.21 (243.475)	1611.55 (892.130)	630.21 (476.420)	961.05 (712.720)
Median	0.00	414.00	780.00	810.00	1544.00	669.15	811.37
Q1, Q3	0.00, 0.00	360.00, 486.00	546.00, 996.00	663.00, 1080.00	927.00, 1877.00	196.52, 908.57	557.00, 1092.00
Min, Max	0.0, 0.0	127.9, 540.0	210.7, 1710.0	561.0, 1350.0	540.0, 3575.0	2.3, 1604.8	25.3, 4984.8
Average burosumab dose per 4-week period (mg)							
Mean (SD)	0.00 (0.000)	67.30 (16.655)	66.96 (16.836)	66.79 (16.241)	59.86 (30.902)	42.59 (26.869)	64.32 (19.962)
Median	0.00	68.25	68.76	60.98	55.72	42.43	63.09
Q1, Q3	0.00, 0.00	59.12, 81.24	52.50, 81.29	51.17, 80.76	40.49, 72.96	18.82, 57.11	50.74, 81.02
Min, Max	0.0, 0.0	21.3, 92.2	13.2, 92.1	50.3, 90.5	18.1, 124.1	2.3, 100.7	8.4, 115.5
Average burosumab dose per 4-week period (mg/kg)							
Mean (SD)	0.00 (0.000)	0.98 (0.088)	0.96 (0.119)	0.99 (0.027)	0.75 (0.268)	0.53 (0.260)	0.91 (0.189)
Median	0.00	1.00	1.00	1.00	0.78	0.55	1.00
Q1, Q3	0.00, 0.00	0.99, 1.01	0.99, 1.00	0.99, 1.00	0.59, 1.00	0.28, 0.79	0.93, 1.00
Min, Max	0.0, 0.0	0.6, 1.0	0.3, 1.0	0.9, 1.0	0.3, 1.0	0.1, 0.8	0.2, 1.0

a: The total burosumab column under UX023-CL303 includes all subjects who ever received any dose of burosumab in Study UX023-CL303. The length of burosumab treatment varies as it includes both subjects randomised to receive burosumab from baseline and subjects randomised to placebo who crossed over to receive burosumab at Week 24.
b: Includes subjects who participated in KRN23-INT-001 only, and subjects who participated in both KRN23-INT-001 and KRN23-INT-002. Twenty of those 28 subjects participated in Study UX023-CL203.
c: The overall burosumab group includes all subjects that have received burosumab in the adult repeat-dose XLH studies, including Study UX023-CL303 subjects randomised to placebo once they crossed over to burosumab. The unique number of subjects in this group is 175; however, 1 subject who enrolled in both KRN23-INT-001 and UX023-CL303 was analysed as 2 different subjects. Details are provided in Section 2.7.4.1.1.2.
The safety analysis set includes all subjects who received at least 1 dose of Investigational Product (burosumab or placebo). Data as of 08 Jun 2017 for ongoing Study UX023-CL303; data as of 08 Jun 2017 for ongoing Study UX023-CL304; data as of 08 Jun 2017 for ongoing Study UX023-CL203.
Max = maximum; Min = minimum; N = total number of subjects who received at least 1 dose of Investigational Product (burosumab or placebo); Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

Adverse events

The treatment emergent adverse events (TEAE) in the adult studies are summarised in Table 38. Adverse events in prespecified areas to monitor are summarised in Table 39.

Table 36: Treatment-emergent Adverse Events: Repeat-dose Studies in Adult XLH

	UX023-CL303			UX023-CL304	UX023-CL203	KRN23-INT-001/002 [b]	Overall Burosumab [c] (N = 176)
	Double-blind Period (Week 0-24)		Total Burosumab (N = 134) [a]	Burosumab (N = 14)	Burosumab (N = 20)	Burosumab (N = 28)	
	Placebo (N = 66)	Burosumab (N = 68)					
Subjects with TEAEs	61 (92.4%)	64 (94.1%)	131 (97.8%)	14 (100.0%)	20 (100.0%)	27 (96.4%)	173 (98.3%)
Maximum severity							
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.0%)	0 (0%)	1 (0.6%)
Grade 3	9 (13.6%)	8 (11.8%)	29 (21.6%)	3 (21.4%)	10 (50.0%)	5 (17.9%)	44 (25.0%)
Grade 2	26 (39.4%)	28 (41.2%)	67 (50.0%)	10 (71.4%)	8 (40.0%)	15 (53.6%)	87 (49.4%)
Grade 1	26 (39.4%)	28 (41.2%)	35 (26.1%)	1 (7.1%)	1 (5.0%)	7 (25.0%)	41 (23.3%)
Subjects with related TEAEs	26 (39.4%)	30 (44.1%)	74 (55.2%)	8 (57.1%)	12 (60.0%)	18 (64.3%)	105 (59.7%)
Subjects with serious TEAEs	2 (3.0%)	2 (2.9%)	15 (11.2%)	2 (14.3%)	9 (45.0%)	3 (10.7%)	28 (15.9%)
Subjects with related serious TEAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.0%)	0 (0%)	1 (0.6%)
Subjects with Grade 3 or 4 TEAEs	9 (13.6%)	8 (11.8%)	29 (21.6%)	3 (21.4%)	11 (55.0%)	5 (17.9%)	45 (25.6%)
Subjects with TEAEs resulting in study discontinuation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (10.7%)	3 (1.7%)
Number of fatal TEAEs	0	0	0	0	0	0	0

For both Table 38 and Table 39:
a: The total burosumab column under UX023-CL303 includes all subjects who ever received any dose of burosumab in Study UX023-CL303. The length of burosumab treatment varies as it includes both subjects randomised to receive burosumab from baseline and subjects randomised to placebo who crossed over to receive burosumab at Week 24.
b: Includes subjects who participated in KRN23-INT-001 only, and subjects who participated in both KRN23-INT-001 and KRN23-INT-002. Twenty of those 28 subjects participated in Study UX023-CL203.
c: The overall burosumab group includes all subjects that have received burosumab in the adult repeat-dose XLH studies, including Study UX023-CL303 subjects randomised to placebo once they crossed over to burosumab. The unique number of subjects in this group is 175; however, 1 subject who enrolled in both KRN23-INT-001 and UX023-CL303 was analysed as 2 different subjects.
The safety analysis set includes all subjects who received at least 1 dose of Investigational Product (burosumab or placebo). Data as of 08 Jun 2017 for ongoing Study UX023-CL303; data as of 08 Jun 2017 for ongoing Study UX023-CL304; data as of 08 Jun 2017 for ongoing Study UX023-CL203. MedDRA version 18.1 was used. Severity was graded according to NCI CTCAE version 4.0 for all studies except UX023-CL304 (version 4.03).
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with an event; N = total number of subjects who received at least 1 dose of Investigational Product (burosumab or placebo); NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event.

Table 37: Treatment-emergent Adverse Events (prespecified areas to monitor): Repeat-dose Studies in ***Adult XLH***

	UX023-CL303			UX023-CL304	UX023-CL203	KRN23-INT-001/002 [b]	
	Double-blind Period (Week 0-24)		Total				
	Placebo (N = 66)	Burosumab (N = 68)	Burosumab (N = 134) [a]	Burosumab (N = 14)	Burosumab (N = 20)	Burosumab (N = 28)	Overall Burosumab [c] (N = 176)
Injection site reactions							
Subjects with TEAEs	8 (12.1%)	8 (11.8%)	27 (20.1%)	5 (35.7%)	6 (30.0%)	9 (32.1%)	44 (25.0%)
Maximum severity							
Grade 2	1 (1.5%)	1 (1.5%)	5 (3.7%)	0 (0%)	0 (0%)	2 (7.1%)	7 (4.0%)
Grade 1	7 (10.6%)	7 (10.3%)	22 (16.4%)	5 (35.7%)	6 (30.0%)	7 (25.0%)	37 (21.0%)
Subjects with related TEAEs	6 (9.1%)	7 (10.3%)	26 (19.4%)	5 (35.7%)	6 (30.0%)	9 (32.1%)	43 (24.4%)
Hypersensitivity							
Subjects with TEAEs	4 (6.1%)	4 (5.9%)	15 (11.2%)	7 (50.0%)	3 (15.0%)	7 (25.0%)	32 (18.2%)
Maximum severity							
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.0%)	0 (0%)	1 (0.6%)
Grade 2	0 (0%)	2 (2.9%)	4 (3.0%)	2 (14.3%)	0 (0%)	2 (7.1%)	8 (4.5%)
Grade 1	4 (6.1%)	2 (2.9%)	11 (8.2%)	5 (35.7%)	2 (10.0%)	5 (17.9%)	23 (13.1%)
Subjects with related TEAEs	0 (0%)	1 (1.5%)	5 (3.7%)	5 (35.7%)	1 (5.0%)	3 (10.7%)	14 (8.0%)
Hyperphosphataemia							
Subjects with TEAEs	0 (0%)	4 (5.9%)	8 (6.0%)	0 (0%)	0 (0%)	0 (0%)	8 (4.5%)
Maximum severity							
Grade 2	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Grade 1	0 (0%)	4 (5.9%)	7 (5.2%)	0 (0%)	0 (0%)	0 (0%)	7 (4.0%)
Subjects with related TEAEs	0 (0%)	4 (5.9%)	8 (6.0%)	0 (0%)	0 (0%)	0 (0%)	8 (4.5%)
Ectopic mineralisation							
Subjects with TEAEs	0 (0%)	0 (0%)	9 (6.7%)	0 (0%)	4 (20.0%)	1 (3.6%)	13 (7.4%)
Maximum severity							
Grade 2	0 (0%)	0 (0%)	3 (2.2%)	0 (0%)	0 (0%)	1 (3.6%)	4 (2.3%)
Grade 1	0 (0%)	0 (0%)	6 (4.5%)	0 (0%)	4 (20.0%)	0 (0%)	9 (5.1%)
Subjects with related TEAEs	0 (0%)	0 (0%)	7 (5.2%)	0 (0%)	2 (10.0%)	1 (3.6%)	10 (5.7%)
Restless legs syndrome							
Subjects with TEAEs	5 (7.6%)	8 (11.8%)	16 (11.9%)	2 (14.3%)	1 (5.0%)	5 (17.9%)	24 (13.6%)
Maximum severity							
Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.6%)	1 (0.6%)
Grade 2	2 (3.0%)	4 (5.9%)	8 (6.0%)	1 (7.1%)	0 (0%)	4 (14.3%)	13 (7.4%)
Grade 1	3 (4.5%)	4 (5.9%)	8 (6.0%)	1 (7.1%)	1 (5.0%)	0 (0%)	10 (5.7%)
Subjects with related TEAEs	4 (6.1%)	8 (11.8%)	14 (10.4%)	2 (14.3%)	1 (5.0%)	2 (7.1%)	19 (10.8%)

Most Frequently Reported Adverse Events

Table 40 summarises the most frequently reported TEAE by SOC in the two treatment arms in study UX023-CL303, in all burosumab treated subjects in UX023-CL303 (i.e. including subjects randomised to placebo after cross-over to burosumab) and in all burosumab treated subjects in the adult clinical development program.

Table 38: Treatment-emergent Adverse Events by System Organ Class and Preferred Term: Repeat-dose Studies of Adult XLH (PTs with Frequency ≥5% Subjects in the Overall Group)

System Organ Class Preferred Term Subject Incidence: n (%)	UX023-CL303 Double-blind Period (Week 0-24) Placebo (N = 66)	UX023-CL303 Double-blind Period (Week 0-24) Burosumab (N = 68)	UX023-CL303 Total Burosumab [a] (N = 134)	Overall Burosumab [b] (N = 176)
Subjects with any TEAE	61 (92.4%)	64 (94.1%)	131 (97.8%)	173 (98.3%)
Infections and infestations	30 (45.5%)	33 (48.5%)	82 (61.2%)	120 (68.2%)
Nasopharyngitis	6 (9.1%)	9 (13.2%)	30 (22.4%)	49 (27.8%)
Tooth abscess	5 (7.6%)	9 (13.2%)	18 (13.4%)	25 (14.2%)
Upper respiratory tract infection	6 (9.1%)	4 (5.9%)	10 (7.5%)	19 (10.8%)
Sinusitis	2 (3.0%)	2 (2.9%)	4 (3.0%)	14 (8.0%)
Urinary tract infection	4 (6.1%)	3 (4.4%)	6 (4.5%)	14 (8.0%)
Influenza	3 (4.5%)	3 (4.4%)	10 (7.5%)	13 (7.4%)
Bronchitis	1 (1.5%)	1 (1.5%)	4 (3.0%)	10 (5.7%)
Musculoskeletal and connective tissue disorders	30 (45.5%)	26 (38.2%)	81 (60.4%)	113 (64.2%)
Arthralgia	16 (24.2%)	6 (8.8%)	32 (23.9%)	53 (30.1%)
Back pain	6 (9.1%)	10 (14.7%)	22 (16.4%)	39 (22.2%)
Pain in extremity	10 (15.2%)	5 (7.4%)	15 (11.2%)	30 (17.0%)
Muscle spasms	2 (3.0%)	5 (7.4%)	12 (9.0%)	21 (11.9%)
Musculoskeletal pain	4 (6.1%)	2 (2.9%)	14 (10.4%)	21 (11.9%)
Bone pain	5 (7.6%)	1 (1.5%)	9 (6.7%)	14 (8.0%)
Myalgia	1 (1.5%)	3 (4.4%)	9 (6.7%)	13 (7.4%)
Joint swelling	0 (0%)	0 (0%)	5 (3.7%)	10 (5.7%)
Musculoskeletal chest pain	0 (0%)	1 (1.5%)	5 (3.7%)	10 (5.7%)
Neck pain	1 (1.5%)	1 (1.5%)	6 (4.5%)	10 (5.7%)
Nervous system disorders	16 (24.2%)	26 (38.2%)	60 (44.8%)	87 (49.4%)
Headache	5 (7.6%)	9 (13.2%)	27 (20.1%)	36 (20.5%)
Restless legs syndrome	4 (6.1%)	8 (11.8%)	15 (11.2%)	22 (12.5%)
Dizziness	4 (6.1%)	7 (10.3%)	10 (7.5%)	20 (11.4%)
Hypoaesthesia	1 (1.5%)	1 (1.5%)	6 (4.5%)	15 (8.5%)
Paraesthesia	1 (1.5%)	0 (0%)	4 (3.0%)	9 (5.1%)
General disorders and administration site conditions	18 (27.3%)	21 (30.9%)	58 (43.3%)	84 (47.7%)
Fatigue	6 (9.1%)	6 (8.8%)	18 (13.4%)	26 (14.8%)
Pain	5 (7.6%)	5 (7.4%)	15 (11.2%)	22 (12.5%)
Injection site reaction	2 (3.0%)	2 (2.9%)	11 (8.2%)	20 (11.4%)
Injection site erythema	2 (3.0%)	3 (4.4%)	8 (6.0%)	12 (6.8%)
Gastrointestinal disorders	18 (27.3%)	20 (29.4%)	51 (38.1%)	81 (46.0%)
Diarrhoea	5 (7.6%)	5 (7.4%)	12 (9.0%)	20 (11.4%)
Nausea	6 (9.1%)	7 (10.3%)	12 (9.0%)	20 (11.4%)
Toothache	1 (1.5%)	3 (4.4%)	15 (11.2%)	18 (10.2%)
Abdominal pain upper	0 (0%)	1 (1.5%)	7 (5.2%)	13 (7.4%)
Constipation	0 (0%)	6 (8.8%)	6 (4.5%)	12 (6.8%)
Abdominal discomfort	0 (0%)	1 (1.5%)	3 (2.2%)	10 (5.7%)
Abdominal pain	2 (3.0%)	1 (1.5%)	5 (3.7%)	10 (5.7%)

Injury, poisoning and procedural complications	14 (21.2%)	12 (17.6%)	34 (25.4%)	61 (34.7%)
Procedural pain	0 (0%)	4 (5.9%)	11 (8.2%)	22 (12.5%)
Fall	0 (0%)	0 (0%)	7 (5.2%)	17 (9.7%)
Investigations [c]	9 (13.6%)	14 (20.6%)	39 (29.1%)	54 (30.7%)
Respiratory, thoracic and mediastinal disorders	11 (16.7%)	11 (16.2%)	29 (21.6%)	50 (28.4%)
Cough	3 (4.5%)	3 (4.4%)	12 (9.0%)	18 (10.2%)
Oropharyngeal pain	7 (10.6%)	1 (1.5%)	7 (5.2%)	13 (7.4%)
Sinus congestion	0 (0%)	1 (1.5%)	3 (2.2%)	9 (5.1%)
Skin and subcutaneous tissue disorders [c]	6 (9.1%)	10 (14.7%)	23 (17.2%)	39 (22.2%)
Metabolism and nutrition disorders	6 (9.1%)	9 (13.2%)	29 (21.6%)	38 (21.6%)
Vitamin D deficiency	3 (4.5%)	5 (7.4%)	14 (10.4%)	16 (9.1%)
Psychiatric disorders	3 (4.5%)	4 (5.9%)	20 (14.9%)	34 (19.3%)
Depression	1 (1.5%)	2 (2.9%)	9 (6.7%)	14 (8.0%)
Insomnia	1 (1.5%)	1 (1.5%)	6 (4.5%)	12 (6.8%)
Renal and urinary disorders [c]	2 (3.0%)	1 (1.5%)	15 (11.2%)	24 (13.6%)
Vascular disorders	5 (7.6%)	3 (4.4%)	15 (11.2%)	24 (13.6%)
Hypertension	2 (3.0%)	2 (2.9%)	7 (5.2%)	11 (6.3%)
Ear and labyrinth disorders [c]	5 (7.6%)	6 (8.8%)	10 (7.5%)	21 (11.9%)
Reproductive system and breast disorders [c]	2 (3.0%)	2 (2.9%)	7 (5.2%)	16 (9.1%)
Cardiac disorders [c]	1 (1.5%)	1 (1.5%)	6 (4.5%)	11 (6.3%)
Immune system disorders	1 (1.5%)	0 (0%)	6 (4.5%)	11 (6.3%)
Seasonal allergy	1 (1.5%)	0 (0%)	5 (3.7%)	9 (5.1%)

a: The total burosumab column under UX023-CL303 includes all subjects who ever received any dose of burosumab in Study UX023-CL303. The length of burosumab treatment varies as it includes both subjects randomised to receive burosumab from baseline and subjects randomised to placebo who crossed over to receive burosumab at Week 24.
b: The overall burosumab group includes all subjects that have received burosumab in the adult repeat-dose XLH studies, including Study UX023-CL303 subjects randomised to placebo once they crossed over to burosumab. The unique number of subjects in this group is 175; however, 1 subject who enrolled in both KRN23-INT-001 and UX023-CL303 was analysed as 2 different subjects. [tradename] (burosumab)
c: No individual Preferred Terms within the System Organ Class had a frequency of ≥5%.
The safety analysis set includes all subjects who received at least 1 dose of Investigational Product (burosumab or placebo). Data as of 08 Jun 2017 for ongoing Study UX023-CL303; data as of 08 Jun 2017 for ongoing Study UX023-CL304; data as of 08 Jun 2017 for ongoing Study UX023-CL203 MedDRA version 18.1 was used.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with an event; N = total number of subjects who received at least 1 dose of Investigational Product (burosumab or placebo); TEAE = treatment-emergent adverse event.

The most frequently reported TEAEs in the Placebo-controlled Treatment Period of Study UX023-CL303 occurred in the following SOCs: Infections and infestations (burosumab: 48.5%; placebo 45.5%); Musculoskeletal and connective tissue disorders (burosumab: 38.2%; placebo: 45.5%); and Nervous system disorders (burosumab: 38.2%; placebo: 24.2%).

The difference between the treatment groups in SOC Nervous system disorders was primarily attributed to the higher incidences of headache, dizziness, and RLS in the burosumab group than in the placebo group.

The imbalance between the treatment groups in SOC Musculoskeletal and connective tissue disorders was primarily attributed to the higher incidence of arthralgia, bone pain and musculoskeletal pain in the placebo group than in the burosumab group. At least twice as many subjects in the placebo group experienced these events compared with the burosumab group.

Overall, across all repeat-dose studies in adults with XLH, the reported TEAEs by SOC followed a similar trend to the burosumab group in Study UX023-CL303 in terms of types and frequency.

Treatment-related TEAEs reported for three or more subjects in either treatment group in Study UX023-CL303 is summarised in Table 41.

Table 39: Treatment-related Treatment-Emergent Adverse Events Reported for Three or More Subjects in Either Treatment Group in the Placebo-controlled Treatment Period (Safety Analysis Set)

Category Subject incidence: n (%)	Placebo (N = 66)	Burosumab (N = 68)
Subjects With Any Related TEAE	26 (39.4)	30 (44.1)
Restless legs syndrome	4 (6.1)	8 (11.8)
Blood phosphorus increased	0	3 (4.4)
Injection site erythema	2 (3.0)	3 (4.4)
Nausea	2 (3.0)	3 (4.4)
Arthralgia	4 (6.1)	1 (1.5)
Bone pain	3 (4.5)	0
Diarrhoea	3 (4.5)	0

The **overall burosumab group** (N = 176) includes all subjects that received burosumab in the adult safety database, including placebo subjects after they crossed over to burosumab in Study UX023-CL303.

TEAEs experienced by ≥10% of subjects in the overall burosumab group were as follows: arthralgia (53 subjects [30.1%]), nasopharyngitis (49 subjects [27.8%]), back pain (39 subjects [22.2%]), headache (36 subjects [20.5%]), pain in extremity (30 subjects [17.0%]), fatigue (26 subjects [14.8%]), tooth abscess (25 subjects [14.2%]), Restless legs (22 subjects [12.5%]), muscle spasms (21 subjects [11.9%]), musculoskeletal pain (21 subjects [11.9%]), pain (21 subjects [11.9%]), diarrhoea (20 subjects [11.4%]), dizziness (20 subjects [11.4%]), injection site reaction (20 subjects [11.4%]), nausea (20 subjects [11.4%]), procedural pain (20 subjects [11.4%]), upper respiratory tract infection (19 subjects [10.8%]), cough (18 subjects [10.2%]) and toothache (18 subjects [10.2%]).

Serious adverse event/deaths/other significant events

Fatal events

There were no TEAEs with an outcome of death through the data cut-off date.

After the data cut-off, one subject in Study UX023-CL303 (Burosumab→burosumab) died in an automobile accident. The Investigator assessed the event as unrelated to burosumab.

Other Serious Adverse Events

Table 42 summarises the SAE reported in the adult studies.

Table 40: Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term: Repeat-dose Studies of Adult XLH

System Organ Class Preferred Term Subject Incidence: n (%)	UX023-CL303 Double-blind Period (Week 0-24) Placebo (N = 66)	UX023-CL303 Double-blind Period (Week 0-24) Burosumab (N = 68)	UX023-CL303 Total Burosumab[a] (N = 134)	Overall Burosumab[b] (N = 176)
Subjects with any serious TEAE	2 (3.0%)	2 (2.9%)	15 (11.2%)	28 (15.9%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (1.5%)	7 (5.2%)	10 (5.7%)
Cervical spinal stenosis	0 (0%)	0 (0%)	1 (0.7%)	2 (1.1%)
Arthralgia	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Back pain	0 (0%)	1 (1.5%)	1 (0.7%)	1 (0.6%)
Joint range of motion decreased	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Musculoskeletal chest pain	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Musculoskeletal pain	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Osteoarthritis	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Pseudarthrosis	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Spinal column stenosis	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Gastrointestinal disorders	0 (0%)	1 (1.5%)	3 (2.2%)	4 (2.3%)
Colitis	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Irritable bowel syndrome	0 (0%)	1 (1.5%)	1 (0.7%)	1 (0.6%)
Periodontal disease	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Small intestinal obstruction	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.5%)	0 (0%)	0 (0%)	4 (2.3%)
Adenocarcinoma of colon	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Breast cancer	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Chordoma	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Lung adenocarcinoma	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Invasive ductal breast carcinoma	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders	0 (0%)	0 (0%)	2 (1.5%)	4 (2.3%)
Migraine	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Myelopathy	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Paraesthesia	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Presyncope	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Hepatobiliary disorders	0 (0%)	0 (0%)	1 (0.7%)	2 (1.1%)
Cholecystitis acute	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Cholelithiasis	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Injury, poisoning and procedural complications	0 (0%)	0 (0%)	2 (1.5%)	2 (1.1%)
Procedural nausea	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Procedural vomiting	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Subdural haematoma	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Cardiac disorders	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Palpitations	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Infections and infestations	1 (1.5%)	0 (0%)	0 (0%)	1 (0.6%)
Medical device site joint infection	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Upper respiratory tract infection	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Angioedema	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Vascular disorders	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Hypertensive crisis	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)

a: The total burosumab column under UX023-CL303 includes all subjects who ever received any dose of burosumab in Study UX023-CL303. The length of burosumab treatment varies as it includes both subjects randomised to receive burosumab from baseline and subjects randomised to placebo who crossed over to receive burosumab at Week 24.
b: The unique number of subjects for the overall burosumab group is 175; however, 1 subject who enrolled in both KRN23-INT-001 and UX023-CL303 was analysed as 2 different subjects. Details are provided in Section 2.7.4.1.1.2. The safety analysis set includes all subjects who received at least 1 dose of Investigational Product (burosumab or placebo). Data as of 08 Jun 2017 for ongoing Study UX023-CL303; data as of 08 Jun 2017 for

ongoing Study UX023-CL304; data as of 08 Jun 2017 for ongoing Study UX023-CL203. Data for Studies KRN23-INT-001 and KRN23-INT-002 are included for subjects who participated in Study KRN23-INT-001 only, and subjects who participated in both studies KRN23-INT-001 and KRN23-INT-002. Twenty of those 28 subjects participated in Study UX023-CL203.

Overall, in Study UX023-CL303, 15 (11.2%) subjects experienced serious TEAEs, none of which was considered by the Investigator as related to study drug.

Through the Placebo-controlled Treatment Period (Week 24) in Phase 3 Study UX023-CL303, 4 subjects experienced SAEs, none of which was assessed by the Investigator as related to study drug.
In the burosumab group, 2 (2.9%) subjects experienced SAEs, 1 each of irritable bowel syndrome and back pain. In the placebo group, 2 (3.0%) subjects experienced SAEs, 1 each of upper respiratory tract infection and invasive ductal breast carcinoma.

After subjects switched from placebo to burosumab, 8 subjects in the placebo→burosumab group experienced SAEs. One subject each experienced cervical spinal stenosis, palpitations, arthralgia, joint range of motion decreased, periodontal disease, presyncope, pseudarthrosis and subdural haematoma. Five subjects in the burosumab→burosumab group had SAEs, including cholelithiasis, colitis, procedural nausea, procedural vomiting, spinal column stenosis, myelopathy and musculoskeletal pain.

As of the data cut-off date of Study UX023-CL303, all SAEs had resolved except for the following: invasive ductal breast carcinoma, myelopathy/spinal column stenosis, and joint range of motion decreased. No SAE is Study UX023-CL303 was considered related to burosumab treatment.

In Studies KRN23-INT-001 and KRN23-INT-002, 3 subjects reported SAEs of cervical spinal stenosis, breast cancer and hypertensive crisis. No SAE was deemed as treatment related.

In Study UX023-CL203, 9 subjects reported SAEs (1 subject each) of musculoskeletal chest pain, osteoarthritis, small intestinal obstruction, colon adenocarcinoma, chordoma, lung adenocarcinoma, cholecystitis acute, medical device site joint infection, and one related SAE of angioedema.

In Study UX023-CL304, 2 subjects experienced SAEs (1 subject each) of migraine and paraesthesia. None of these were deemed as related by the Investigator.

No action was taken with respect to study drug administration in any of the SAE cases.

Narratives

Narratives from selected SAEs reported in burosumab treated adult subjects before data cut-off for this application are summarised below.

Serious Adverse Events in KRN23-INT-001 and KRN23-INT-002

Subject: Breast Cancer

One subject with XLH treated with burosumab in both study KRN23-INT-001 (four doses) and KRN23-INT-002 (12 doses). The last dose was administered on Study Day 311.
On Study Day 271, the subject experienced a SAE of breast cancer. No action was taken with respect to study drug administration.

The event of breast cancer was considered by the Investigator to be unlikely related to the study drug.

Serious Adverse Events in UX023-CL203

Subject: Angioedema

A treatment-related serious, life-threatening event of angioedema was reported in a subject enrolled in Study UX023-CL203. The subject's concomitant medications included lisinopril. The subject commenced treatment with subcutaneous burosumab every 4 weeks. On Study Day 392, the subject experienced

symptoms of throat tightening and swollen face and tongue. The lisinopril was discontinued. Upon rechallenge with burosumab approximately 4 weeks after the event, the angioedema did not recur.

The Investigator assessed the event as possibly related to both burosumab and lisinopril. As the case was heavily confounded by co-suspect ACE inhibitor and the subject continued on study medication without rechallenge hypersensitivity reactions, the MAH considered the event related to lisinopril and unrelated to burosumab.

Subject: Lung Adenocarcinoma

Lung adenocarcinoma was reported in a subject. The subject never used tobacco or smokeless tobacco; however, family history was significant for lung cancer in a parent.
During the study screening period, the subject was found to have a possible left lung nodule on their anteroposterior chest x-ray. The subject commenced study treatment with subcutaneous burosumab. After a comprehensive work-up, the nodule was diagnosed as adenocarcinoma. No action was taken with study drug in response to the event and treatment with burosumab remained ongoing.

The Investigator assessed the event as CTCAE Grade 3 (severe) and not related to the study drug. The MAH assessed the event as not related to burosumab.

Subject: Chordoma

A subject experienced an SAE of "chordoma". On Study Day 673, a renal ultrasound showed a right parenchymal mass and a left partially exophytic mass. On Study Day 689, CT of abdomen and pelvis revealed a large mass arising from sacrum containing chondroid matrix; and a right renal mass and a left renal mass. On Study Day 718, biopsy result revealed chordoma. The Investigator explained that chordoma is a rare type of cancerous tumour that can occur anywhere along the spine. No action was taken with burosumab in the management of the event, and the treatment was ongoing.

Investigator assessed the event of chordoma as CTCAE Grade 3 (severe) and unrelated to burosumab. Cancer was considered as alternate aetiology.

Subject: Adenocarcinoma of Colon

One subject, who experienced a serious TEAE of adenocarcinoma of the colon, 540 days after their first dose of burosumab. The subject's family history included parents and grandparents with cancer; and positive family history of genetic mutations for BRCA2, MSH2 as well as others. Genetic analysis of the subject showed variant of unknown clinical significance in MSH-2 gene. No action was taken with burosumab in the management of the event.

The event was assessed by the Investigator as CTCAE Grade 3 (severe) in severity and unlikely related to study drug.

Serious Adverse Events in UX023-CL303

Subject (Placebo→burosumab): Presyncope (complex partial epilepsy)

One subject, experienced a serious TEAE of Presyncope (verbatim: complex partial epilepsy) beginning on Study Day 179, 13 days after their first dose of burosumab. The subject was hospitalised and was diagnosed with complex partial epilepsy. Medical history included seizure whilst eclamptic during pregnancy. The subject was prescribed multiple medications that could have played contributory roles for the reported event of partial seizures.

The event was assessed by the Investigator as mild (Grade 1) in severity and probably not related to study drug. Although seizure episodes continued, there was no disruption of study treatment.

The subject was hospitalised again at Study Day 468 (after data cut-off), The subject had been experiencing symptoms for over a year. These spells were recorded as near syncope, severe weakness and complex partial epilepsy. The treating physicians could not agree on aetiology of the symptoms. No action was taken with study drug in the management of the event, and the treatment was ongoing. Confounders in diagnosis and concomitant medication.

Subject (Burosumab→burosumab): Spinal column stenosis and Myelopathy

A subject experienced SAEs of Spinal column stenosis and Myelopathy (verbatim terms: "worsening spinal stenosis", "acute myelopathy"). In addition to XLH, the subject's medical history included: multilevel spinal stenosis, laminectomy ossification of the posterior longitudinal ligament, and hypertension. On Study Day 170, during the Week 24 visit 6-minute walk test, the subject first noted that they were weaker than had been previously. Over the following weeks the symptoms worsened. On Study Day 218, a new MRI showed multiple pathologies. The subject was subsequently subjected to surgery. No action was taken with burosumab in the management of the events, and the treatment was ongoing.

The Investigator assessed the events of worsening spinal stenosis and acute myelopathy as important medical events resulting in hospitalisation, the event of worsening spinal stenosis as CTCAE Grade 3 (severe) and the event of acute myelopathy as CTCAE Grade 2 (moderate). Both events were assessed as unlikely related to the blinded study drug, but instead to the subject's pre-existing multilevel spinal stenosis related to XLH.

After data cut-off, the subject presented with restenosis. The Investigator considered that the cadence of the restenosis the subject experienced was more rapid than if it occurred as a result of baseline disease. Since the subject had a rapid restenosis twice while on study medication, the Investigator considered the event might have been possibly related to the study medication administration.

Other Significant Adverse Events: Injection Site Reactions (ISR)

The subject incidence of ISRs across all paediatric studies was 58.5% with an exposure adjusted event incidence/year of 1.987.

The incidence of ISRs in the adult studies are given in Table 43.

*Table 41: Treatment-emergent Injection Site Reactions – Study UX023-CL303 and Overall Repeat-dose Studies in **Adult XLH***

Preferred Term Subject Incidence: n (%)	UX023-CL303 Double-blind Period (Week 0-24) Placebo (N = 66)	 Burosumab (N = 68)	Total Burosumab [a] (N = 134)	Overall Burosumab [b] (N = 176)
Number of ISR TEAEs	9	12	74	164
Number of subjects with ISR TEAEs	8 (12.1%)	8 (11.8%)	27 (20.1%)	44 (25.0%)
Maximum severity				
Grade 2	1 (1.5%)	1 (1.5%)	5 (3.7%)	7 (4.0%)
Grade 1	7 (10.6%)	7 (10.3%)	22 (16.4%)	37 (21.0%)

a: The total burosumab column under UX023-CL303 includes all subjects who ever received any dose of burosumab in Study UX023-CL303. The length of burosumab treatment varies as it includes both subjects randomised to receive burosumab from baseline and subjects randomised to placebo who crossed over to receive burosumab at Week 24.

b: The overall burosumab group includes all subjects that have received burosumab in the adult repeat-dose XLH studies, including Study UX023-CL303 subjects randomised to placebo once they crossed over to burosumab. The unique number of subjects in this group is 175; however, 1 subject who enrolled in both KRN23-INT-001 and UX023-CL303 was analysed as 2 different subjects.

Across all adult studies, the subject incidence of ISRs was 25% and the exposure-adjusted event incidence was 0.796 events/year. Overall, most ISRs were Grade 1 (86%), occurred within 1 day of drug administration (93%), lasted about 1 to 3 days, and resolved as of the data cut-off dates (99%).

Other Significant Adverse Events: Hypersensitivity

Across all paediatric studies, the methodology of using the narrow "Hypersensitivity" SMQ identified 28 paediatric subjects (43%) with 56 TEAE PTs that could indicate a possible hypersensitivity reaction. Hypersensitivity TEAEs were considered to be at least possibly related to treatment for 8 subjects (12%). The most frequent treatment-related hypersensitivity TEAEs were injection site rash (6.2%), rash (3.1%) and urticaria (3.1%).

Across all repeat-dose adult studies, 55 hypersensitivity TEAEs were reported for 33 (18.8%) subjects (Table 44). One subject in Study UX023-CL203 reported 1 serious, Grade 4 (life-threatening) event of angioedema discussed above.

*Table 42: Treatment-emergent Hypersensitivity Adverse Events – Study UX023-CL303 and Overall Repeat-dose Studies in **Adult XLH***

	UX023-CL303			
	Double-blind Period (Week 0-24)		Total Burosumab (N = 134) [a]	Overall Burosumab [b] (N = 176)
Preferred Term Subject Incidence: n (%)	Placebo (N = 66)	Burosumab (N = 68)		
Number of hypersensitivity TEAEs	4	4	28	55
Number of subjects with hypersensitivity TEAEs	4 (6.1%)	4 (5.9%)	15 (11.2%)	33 (18.8%)
Maximum severity				
Grade 4	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Grade 2	0 (0%)	2 (2.9%)	4 (3.0%)	8 (4.5%)
Grade 1	4 (6.1%)	2 (2.9%)	11 (8.2%)	24 (13.6%)

For footnotes, please refer to Table 43

Because the narrow SMQ for "hypersensitivity" is a relatively wide search criteria, another targeted search was conducted for severe hypersensitivity events using PTs in narrow SMQs 'Severe cutaneous adverse reactions', 'Anaphylactic reaction', and 'Angioedema'.

This search yielded 9 subjects who reported 10 TEAEs: urticaria (3 subjects [1.7%]), gingival swelling (2 subjects [1.1%]), swelling face (2 subjects [1.1%]), angioedema (1 subject [0.6%]), and swollen tongue (1 subject [0.6%]).

Narratives were presented for these events, however, not included in the AR for the sake of conciseness. The Investigators assessed all events except angioedema as unrelated to study treatment and burosumab was not withdrawn in any of the cases.

Other Significant Adverse Events: Hyperphosphataemia

No TEAEs of hyperphosphataemia (i.e., a serum phosphorus above the upper limit of normal [ULN] for age) or blood phosphorus increased were identified in any of the paediatric subjects.

In adult studies, eight subjects reported nine events of hyperphosphataemia (>4.5 mg/dL), all in Study UX023-CL303 (Table 45). Most hyperphosphataemia TEAEs were assessed by the Investigator as mild (Grade 1) in severity, and none were serious or associated with study discontinuation. 5/8 subjects with

hyperphosphataemia required protocol-specified dose reductions. For 4/5 subjects, reduction from 1.0 to 0.5 mg/kg was sufficient. However, in one of the subjects an additional dose reduction to 0.25 mg/kg was required.

Table 43: Hyperphosphataemia Events – Study UX023-CL303 and Overall Repeat-dose Studies in Adult XLH

	UX023-CL303			Overall Burosumab [b] (N = 176)
	Double-blind Period (Week 0-24)			
Preferred Term Subject Incidence: n (%)	Placebo (N = 66)	Burosumab (N = 68)	Total Burosumab (N = 134) [a]	
Number of hyperphosphataemia TEAEs	0	5	9	9
Number of subjects with hyperphosphataemia TEAEs	0 (0%)	4 (5.9%)	8 (6.0%)	8 (4.5%)
Maximum severity				
Grade 2	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Grade 1	0 (0%)	4 (5.9%)	7 (5.2%)	7 (4.0%)

For footnotes, please refer to Table 43

Other Significant Adverse Events: Ectopic Mineralisation

In Study UX023-CL303, through the Placebo-controlled Treatment Period (Week 24), there were no TEAEs associated with ectopic mineralisation. The overall Ectopic Mineralization TEAEs are summarised in Table 46.

Table 44: Treatment-emergent Ectopic Mineralisation Adverse Events – Study UX023-CL303 and Overall Repeat-dose Studies in Adult XLH

	UX023-CL303			Overall Burosumab [b] (N = 176)
	Double-blind Period (Week 0-24)		Total Burosumab [a] (N = 134)	
Preferred Term Subject Incidence – n (%)	Placebo (N = 66)	Burosumab (N = 68)		
Number of ectopic mineralisation TEAEs	0	0	9	14
Number of subjects with ectopic mineralisation TEAEs	0 (0%)	0 (0%)	9 (6.7%)	13 (7.4%)
Maximum severity				
Grade 2	0 (0%)	0 (0%)	3 (2.2%)	4 (2.3%)
Grade 1	0 (0%)	0 (0%)	6 (4.5%)	9 (5.1%)
Nephrocalcinosis	0 (0%)	0 (0%)	6 (4.5%)	6 (3.4%) c
Nephrolithiasis	0 (0%)	0 (0%)	3 (2.2%)	6 (3.4%) d
Pancreatic calcification	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)

a: The total burosumab column under UX023-CL303 includes all subjects who ever received any dose of burosumab in Study UX023-CL303. The length of burosumab treatment varies as it includes both subjects randomised to receive burosumab from baseline and subjects randomised to placebo who crossed over to receive burosumab at Week 24. b: The overall burosumab group includes all subjects that have received burosumab in the adult repeat-dose XLH studies, including Study UX023-CL303 subjects randomised to placebo once they crossed over to burosumab. The unique number of subjects in this group is 175; however, 1 subject who enrolled in both KRN23-INT-001 and UX023-CL303 was analysed as 2 different subjects.. c: Based on renal ultrasound observations at Week 24, 3 subjects reported TEAEs of nephrocalcinosis on the same day that they received their first dose of burosumab. d: Based on renal ultrasound observations at Week 24, 1 subject reported a TEAE of nephrolithiasis on the same day that the subject received their first dose of burosumab

Through the data cut-off date, 9 subjects (6.7%) experienced TEAEs of nephrocalcinosis (6 subjects) or nephrolithiasis (3 subjects). The exposure-adjusted event incidence in the total burosumab group was 0.08 events/year.

These events were noted at the Weeks 24 and 48 visits and were based on renal ultrasound assessments. At Week 24, TEAEs of nephrocalcinosis were reported for 4 subjects (placebo group: 3; burosumab group: 1), and TEAEs of nephrolithiasis were reported for 3 subjects (placebo group: 1; burosumab group: 2).
At Week 48, TEAEs of nephrocalcinosis were reported for 2 subjects (1 subject each in the placebo→burosumab and burosumab→burosumab groups).

In the 4 subjects in the placebo group, the TEAEs of nephrocalcinosis and nephrolithiasis occurred on the same day as the first dose of open-label burosumab at Week 24 and are therefore considered burosumab-emergent. While 3 of these 4 events were considered treatment-related by the investigator, a causal association to burosumab was highly unlikely given exposure of less than 1 day.

One subject in Study KRN23-INT-002 experienced Grade 2 nephrolithiasis, which was considered related to treatment by the Investigator. However, the event was confounded by the subject's pre-existing nephrocalcinosis and history of nephrolithiasis.
In Study UX023-CL203, most subjects had no nephrocalcinosis on renal ultrasound at baseline (75.0%) or at Week 48 (80.0%) of burosumab treatment. One (5.0%) subject had Grade 1 nephrocalcinosis at baseline and no nephrocalcinosis at Week 48, 1 (5.0%) subject had Grade 1 nephrocalcinosis at both visits, 2 (10.0%) subjects had Grade 2 nephrocalcinosis at both visits, and 1 (5.0%) subject had a nonreadable renal ultrasound at baseline and Grade 1 nephrocalcinosis at Week 48 of burosumab treatment.
No subjects in Study UX023-CL304 had an ectopic mineralisation TEAE.

Nephrocalcinosis detected by renal ultrasound was scored using a 5-point scale in which 0 = normal and 4 = stone formation. Renal ultrasound scores were assessed by the last available value on study because it better reflects variability of clinical ultrasound readings and also captures those subjects who had unchanged scores at initial assessments but subsequently had decreases in scores on study.

No subjects had changes of more than 1 point in Study UX023-CL303 (Table 47).

Table 45: Shifts in Nephrocalcinosis Scores to Last Post-baseline Grade by Renal Ultrasound In Study UX023-CL303 (Safety Analysis Set)

			UX023-CL303		
			Double-blind Period (Week 0-24)		
	Baseline Grade	Last Post-Baseline Grade	Placebo (N = 66)	Burosumab (N = 68)	Total Burosumab [a] (N = 134)
Baseline	0		27 (40.9%)	34 (50.0%)	61 (45.5%)
	1		32 (48.5%)	23 (33.8%)	55 (41.0%)
	2		7 (10.6%)	9 (13.2%)	16 (11.9%)
	3		0 (0%)	2 (2.9%)	2 (1.5%)
Post-Baseline	0	1	9 (13.6%)	9 (13.2%)	16 (11.9%)
	0	0	18 (27.3%)	23 (33.8%)	44 (32.8%)
	0	NA	0 (0%)	2 (2.9%)	1 (0.8%)
	1	2	3 (4.5%)	1 (1.5%)	6 (4.5%)
	1	1	26 (39.4%)	18 (26.5%)	46 (34.3%)
	1	0	3 (4.5%)	4 (5.9%)	3 (2.2%)
	2	3	0 (0%)	1 (1.5%)	1 (0.8%)
	2	2	6 (9.1%)	8 (11.8%)	13 (9.7%)
	2	1	1 (1.5%)	0 (0%)	2 (1.5%)
	3	3	0 (0%)	1 (1.5%)	2 (1.5%)
	3	NA	0 (0%)	1 (1.5%)	0 (0%)
Summary					
Unchanged	-	-	50 (75.8%)	50 (73.5%)	105 (78.4%)
Shift +1 grade	-	-	12 (18.2%)	11 (16.2%)	23 (17.2%)
Shift -1 grade	-	-	4 (6.1%)	4 (5.9%)	5 (3.7%)
Not calculable	-	-	0 (0%)	3 (4.4%)	1 (0.7%)

a: The total burosumab column under UX023-CL303 includes all subjects who ever received any dose of burosumab in Study UX023-CL303. The length of burosumab treatment varies as it includes both subjects randomised to receive burosumab from baseline and subjects randomised to placebo who crossed over to receive burosumab at Week 24.

Renal ultrasound scores in Studies UX023-CL203 and UX023-CL304 showed a similar pattern. Scores were unchanged from baseline to the last available assessment for 18/20 subjects (90%) in Study UX023-CL203 and 12/14 subjects (85.7%) in Study UX023-CL304.
For subjects with changes in renal ultrasound scores during treatment, increases or decreases in scores were 1 point; no subjects had changes of more than 1 point. The maximum last post-baseline score was 3 in 2 subjects: a +1 shift for 1 subject (baseline score of 2), and unchanged for 1 subject (baseline score of 3).

In Study UX023-CL303, cardiac echogram (ECHO) was also performed to evaluate for potential changes in cardiac ectopic mineralisation or left ventricular hypertrophy (LVH). Ectopic mineralisation was scored with a semi-quantitative echocardiographic calcium score (eCS) (Gaibazzi et al, 2014). The majority of subjects (88.8%) entered the study with no evidence of ectopic mineralisation (ie, eCS = 0); most (79.1%) maintained an eCS of 0 at Week 24 and at Week 48 (83.6%) (Table 48).

Table 46: Shift of Echocardiogram Ectopic Mineralization Grade by Visit UX023-CL303 ***adult XLH*** *Safety Analysis Set - Week 48 Analysis*

Visit	Baseline Value	Post-baseline Value	Placebo -> KRN23 (N=66) n (%)	KRN23 -> KRN23 (N=68) n (%)	Total (N=134) n (%)
Baseline					
	Grade 0		59 (89.4)	60 (88.2)	119 (88.8)
	Grade 1		5 (7.6)	7 (10.3)	12 (9.0)
	Missing		2 (3.0)	1 (1.5)	3 (2.2)
Week 24					
	Grade 0	Grade 1	7 (10.6)	1 (1.5)	8 (6.0)
	Grade 0	Grade 0	50 (75.8)	56 (82.4)	106 (79.1)
	Grade 0	Missing	2 (3.0)	3 (4.4)	5 (3.7)
	Grade 1	Grade 1	4 (6.1)	4 (5.9)	8 (6.0)
	Grade 1	Grade 0	1 (1.5)	3 (4.4)	4 (3.0)
	Missing	Grade 1	1 (1.5)	0	1 (0.7)
	Missing	Grade 0	1 (1.5)	1 (1.5)	2 (1.5)
		Change from Baseline >=2 Grade	0	0	0
Week 48					
	Grade 0	Grade 1	3 (4.5)	1 (1.5)	4 (3.0)
	Grade 0	Grade 0	56 (84.8)	56 (82.4)	112 (83.6)
	Grade 0	Missing	0	3 (4.4)	3 (2.2)
	Grade 1	Grade 1	3 (4.5)	3 (4.4)	6 (4.5)
	Grade 1	Grade 0	2 (3.0)	4 (5.9)	6 (4.5)
	Missing	Grade 1	1 (1.5)	0	1 (0.7)
	Missing	Grade 0	1 (1.5)	0	1 (0.7)
	Missing	Missing	0	1 (1.5)	1 (0.7)
		Change from Baseline >=2 Grade	0	0	0

A subject in Study UX023-CL304 experienced a TEAE of ejection fraction (EF) decreased at Week 48. The subject had an ejection fraction of 77.1% at baseline, 77.4% at Week 24, and 65.7% at Week 48. Although an ejection fraction of 65% is within normal limits, the Investigator considered the decreased EF as a TEAE. The reading cardiologist noted no significant change from the prior ECHO. The event was mild in severity and considered not related to study drug by the Investigator. The event was not resolved as of the data cut-off date.

Other Significant Adverse Events: Restless legs (RLS)

The exact mechanism of RLS in XLH subjects treated with burosumab is not known. It is hypothesised that increasing serum phosphorus levels near/into the normal range in subjects that have been chronically and severely hypophosphataemic may precipitate RLS symptoms/severity. Studies in chronic kidney disease (CKD) patients, who have a high frequency of RLS, have shown that higher serum phosphorus levels are strongly associated with RLS and that lowering serum phosphorus through dialysis will immediately reduce or eliminate RLS symptoms.

RLS has not been observed in subjects in the paediatric studies.

A total of 4 (3%) subjects (2 in each treatment group) entered the placebo-controlled Phase 3 study, UX023-CL303, with a documented medical history of RLS. Two of these subjects (1 in each treatment group) experienced worsening RLS reported as a TEAE. Subject-level details of RLS events in adult studies are provided in the table below.

*Table 47: Treatment-emergent RLS Adverse Events – Study UX023-CL303 and Overall Repeat-dose Studies in **Adult XLH***

Preferred Term Subject Incidence: n (%)	UX023-CL303 Double-blind Period (Week 0-24) Placebo (N = 66)	 Burosumab (N = 68)	 Total Burosumab (N = 134) [a]	Overall Burosumab (N = 176) [b]
Number of restless legs syndrome TEAEs	5	8	16	28
Number of subjects with restless legs syndrome TEAEs	5 (7.6%)	8 (11.8%)	16 (11.9%)	24 (13.6%)
Maximum severity				
Grade 3	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Grade 2	2 (3.0%)	4 (5.9%)	8 (6.0%)	13 (7.4%)
Grade 1	3 (4.5%)	4 (5.9%)	8 (6.0%)	10 (5.7%)
Restless legs syndrome	4 (6.1%)	8 (11.8%)	15 (11.2%)	22 (12.5%)
Akathisia	0 (0%)	0 (0%)	1 (0.7%)	1 (0.6%)
Limb discomfort c	1 (1.5%)	0 (0%)	0 (0%)	1 (0.6%)

For footnotes, please refer to Table 43

One subject, in Study KRN23-INT-002, experienced a TEAE of worsening RLS, Grade 3 in severity, which led to discontinuation from the study. The RLS resolved/returned to baseline level after discontinuing burosumab. This subject subsequently enrolled in Study UX023-CL203 and had not reported RLS after more than 48 weeks of treatment.

Other Significant Adverse Events: Anti-burosumab Antibodies

Summary of Immunogenicity in Paediatric Subjects

In total, of the 94 subjects who were treated with burosumab, 86 (91.5%) subjects were ADA negative (79 subjects negative at all timepoints; 7 baseline positive subjects who did not have a boosted ADA response) and 8 (8.5%) subjects were ADA positive. There were 3 (3.2%) paediatric subjects who were considered to be positive for neutralising antibodies (Nab).

Immunogenicity Results in Adults: Study UX023-CL303

Before initiation of burosumab treatment in Study UX023-CL303, the majority of subjects were negative for ADA (114/134; 85.1%).

Table 48: ADA Results in Adult Subjects with XLH (Study UX023-CL303)

Baseline Result	Results After Initiation of Burosumab [a]	Placebo Group[a] (N = 66)	Burosumab Group (N = 68)	Total Burosumab (N = 134)
Negative	Negative at All Visits After Initiation of Burosumab	52 (78.8%)	54 (79.4%)	106 (79.1%)
	Positive at Any Visit After Initiation of Burosumab	4 (6.1%)	4 (5.9%)	8 (6.0%)
Positive	Negative at All Visits After Initiation of Burosumab	3 (4.5%)	4 (5.9%)	4 (5.2%)
	Positive at Any Visit After Initiation of Burosumab	7 (10.6%)	6 (8.8%)	13 (9.7%)

ADA = antidrug antibody; n = number of subjects who tested positive or negative for anti-drug antibodies; N = total number of subjects who received at least 1 dose of Investigational Product (burosumab or placebo); XLH = X-linked hypophosphatemia. a: Subjects randomised to placebo crossed over to burosumab treatment at Week 24; all subjects received open-label burosumab after Week 24. Samples for assessment of ADA were drawn before the dose of burosumab for the visit.

Eight subjects who were negative at baseline were positive for ADA (titre ≥2) at least 1 visit after initiation of burosumab treatment (i.e., treatment-induced ADAs). These subjects had transient immune responses, with ADA-positive samples at only 1 or 2 post-treatment time points.

Of the 20 subjects positive for ADA before initiation of burosumab treatment, 7 were negative for ADA after initiation of burosumab treatment, and 13 were positive for ADA at ≥1 visit after initiation of burosumab treatment; all of the 13 subjects showed decreased or unchanged titre post-treatment, i.e., treatment did not boost ADA response.

All samples positive for ADA in the improved assay were tested in the NAb assay. All NAb results in Study UX023-CL303 were negative, i.e., no neutralising activity was detected.

Immunogenicity Results in Adults: Study UX023-CL304

In study UX023-304, of the 14 subjects treated with burosumab in study, 4 subjects (28.6%) had ADA positive samples at baseline, while 10 (71.4%) subjects were ADA negative.
The 10 subjects, who were ADA negative at baseline, remained ADA negative throughout the study. Of the 4 subjects who had ADA positive samples at baseline, 2 subjects did not have ADA positive samples detected post-baseline, while 2 subjects had samples that were not confirmed to be ADA positive. Therefore, none of the 14 subjects were determined to be ADA positive during the study.

Impact on Immunogenicity on Efficacy in Adult Subjects (Study UX023-CL303)

The potential impact of ADA on efficacy in adults with XLH was assessed by a review of changes in serum phosphorus concentrations for the 28 subjects positive for ADA at any point in Study UX023-CL303 (Table 51).

Table 49: Serum Phosphorus Concentrations in the Overall Study Population by Treatment Group for the Overall Study

		Serum Phosphorus Concentration (mg/dL)					
		Placebo			Burosumab		
Visit	Statistic	Overall (N = 66)	ADA+ at Baseline or Any Postbaseline Visit (N = 14)	ADA+ After Burosumab Initiation (N = 4[a])	Overall (N = 68)	ADA+ at Baseline or Any Postbaseline Visit (N = 14)	ADA+ After Burosumab Initiation (N = 4[b])
Baseline	Mean (SD) [n]	1.92 (0.316) [66]	1.83 (0.284) [14]	1.55 (0.265) [4]	2.03 (0.304) [68]	2.05 (0.409) [14]	2.05 (0.129) [4]
Week 22 (peak PD effect)	Mean (SD) [n]	2.03 (0.294) [65]	1.97 (0.320) [13]	1.83 (0.404) [3]	2.91 (0.549) [64]	2.75 (0.514) [14]	2.83 (0.556) [4]
	Mean (SD) change from Baseline [n]	+0.10 (0.286) [65]	+0.10 (0.346) [13]	+0.20 (0.346) [3]	+0.88 (0.521) [64]	+0.70 (0.447) [14]	+0.78 (0.550) [4]
Week 24 (trough PD effect)	Mean (SD) [n]	2.07 (0.343) [66]	2.04 (0.373) [14]	1.78 (0.340) [4]	2.53 (0.446) [68]	2.46 (0.521) [14]	2.43 (0.377) [4]
	Mean (SD) change from Baseline [n]	+0.15 (0.346) [66]	+0.21 (0.354) [14]	+0.23 (0.171) [4]	+0.49 (0.395) [68]	+0.41 (0.346) [14]	+0.38 (0.330) [4]
		Placebo → Burosumab[c]			Burosumab → Burosumab[c]		
Week 46 (peak PD effect)	Mean (SD) [n]	3.03 (0.532) [66]	2.93 (0.432) [14]	2.88 (0.763) [4]	2.99 (0.549) [65]	2.75 (0.585) [14]	2.63 (0.618) [4]
	Mean (SD) change from Baseline [n]	+1.11 (0.513) [66]	+1.10 (0.456) [14]	+1.33 (0.665) [4]	+0.94 (0.548) [65]	+0.65 (0.433) [14]	+0.58 (0.591) [4]
Week 48 (trough PD effect)	Mean (SD) [n]	2.47 (0.494) [66]	2.19 (0.436) [14]	1.93 (0.556) [4]	2.48 (0.456) [64]	2.41 (0.589) [13]	2.35 (0.695) [4]
	Mean (SD) change from Baseline [n]	+0.54 (0.482) [66]	+0.36 (0.386) [14]	+0.38 (0.320) [4]	+0.45 (0.454) [64]	+0.35 (0.595) [14]	+0.30 (0.688) [4]

ADA+ = positive for burosumab antidrug antibody, N = number of subjects in group, n = number of subjects with serum phosphorus values at indicated time, NAb = neutralising antibodies; PD = pharmacodynamics; SD = standard deviation.
a: ADA negative at Baseline and positive after initiation of burosumab: Subjects 156-311, 162-002, 186-310, 207-302
b: ADA negative at Baseline and positive after initiation of burosumab: Subjects 138-309, 139-309, 162-305, 194-301
c: Subjects randomised to the placebo group crossed over to burosumab treatment at Week 24 (placebo → burosumab); subjects in the burosumab group continued to receive burosumab after Week 24 (placebo → burosumab). All subjects received open-label burosumab after Week 24.

Impact on Immunogenicity on Safety in Adult Subjects (Study UX023-CL303)

Of the 28 subjects positive for ADA at Baseline or any postbaseline visit in Study UX023-CL303:

- Twenty subjects did not have burosumab-emergent ISRs or AEs of hypersensitivity
- Five subjects had burosumab-emergent ISRs:
    - Injection site pruritus
    - Injection site pruritus, Injection site erythema
    - Injection site reaction, Injection site erythema
    - Injection site erythema
    - Injection site reaction, Injection site pruritus

  All ISRs for these subjects were non-serious, mild (Grade 1) or moderate (Grade 2) in severity and resolved on study. All were considered by the Investigators to be related to burosumab. None of these ISRs resulted in change to the burosumab dose or discontinuation from study.
- One subject had a burosumab-emergent AE of hypersensitivity. The subject had a non-serious event of mild (Grade 1) contact dermatitis that was considered by the Investigator to be possibly related to burosumab. The event resolved on study, did not result in a change to the burosumab dose or discontinuation from study.
- Two subjects each had an event of injection site hypersensitivity. These events were non-serious, mild (Grade 1) in severity, resolved on study and were considered by the Investigators to be

related to burosumab. Neither of these ISRs resulted in change to the burosumab dose or discontinuation from study.

In addition, these subjects had other AEs of hypersensitivity: rash (2 events) for one subject, and hypersensitivity and eczema (2 events) for another subject. These events were non-serious, mild (Grade 1) or moderate (Grade 2) in severity, did not result in a change to the burosumab dose or discontinuation from study. These events were considered by the Investigators to be not related to burosumab except for1 event of rash that was considered possibly related. These AEs of hypersensitivity resolved on study, except for an event of eczema that was resolving at end of study.

Events of ISRs and/or hypersensitivity were not necessarily coincident with the timing of samples testing positive for ADA, and no correlation between the occurrence of ISR, hypersensitivity AEs, and ADA was evident. Overall, ISRs and hypersensitivity-like reactions in subjects positive for ADA at Baseline or any post-baseline visit were non-serious, mild-to-moderate in severity, and resolved on study (with exception of 1 event that was reversing). The safety and benefit-risk profiles for these subjects were similar to those of subjects negative for ADA. These results suggest that immunogenicity, i.e., the presence of anti-burosumab antibodies, does not impact the safety of burosumab in adults with XLH.

Laboratory findings

Overall, analysis of laboratory data (serum phosphorus, iPTH, serum calcium, eGFR, serum creatinine or BUN and serum amylase) did not reveal any clinically meaningful safety concerns in the paediatric studies. Results from the adult studies are summarised below.

Serum Phosphorus

Hyperphosphataemia, as defined by a serum phosphorus level above the ULN (4.5 mg/dL; 1.5 mmol/L), has been observed in repeat-dose adult studies. The observed serum phosphorus levels in these studies were below the dose limiting toxicity threshold of 6.5 mg/dL (2.1 mmol/L).

Events of high serum phosphorus in UX023-CL303 is summarised in Table 52.

Table 50: Subject-level Detail of High Serum Phosphorous (mg/mL) in Study UX023-CL303 (Safety Analysis Set)

Group	Baseline (mg/dL)	Elevated Value (mg/dL) (Visit)	Return to Reference Range (Visit)	TEAE? (Duration; Outcome)	Protocol-specified Action	Burosumab Dose Reduction (Duration)
Burosumab	2.0 (LOW)	5.0 (W2)	W4-6	No	None	None
		4.9 (W10)	W12	Yes (170 days; recovered)	Dose reduction	0.5 mg/kg (W12-48+)
Burosumab	3.0	4.7 (W6)	W10-12	No	None	None
		5.4 (W14)	W18	Yes (85 days; recovered)	Dose reduction	0.5 mg/kg (W16-52+)
Burosumab	2.3 (LOW)	6.2 (W1) 6.2 (W2)	W4	Yes (224 days; recovered)	Dose reduction	0.5 mg/kg (W4-56+)
Burosumab	2.3 (LOW)	4.7 (W2)	W4	No	None	None
		4.7 (W10)	W12	No	Dose reduction	0.5 mg/kg (W12-60+)
Burosumab	2.0 (LOW)	5.0 (W4) 5.5 (W6) 5.0 (W8) 5.4 (W10) 4.6 (W12)	W14	Yes (29 days; recovered)	Dose reduction (W8)/ Dose skipped (W12)	0.5 mg/kg (W8-16)
		4.6 (W18)	W20	Yes (15 days; recovered)	Dose reduction	0.25 mg/kg (W20-60+)
Burosumab	2.5	4.8 (W6)	W10	No	None	None
Burosumab	2.5	5.0 (W1)	W4	No	None	None
Burosumab	1.9 (LOW)	4.9 (W18)	W20	No	None	None
Burosumab	1.4 (LOW)	4.9 (W6)	W10	No	None	None
Placebo	2.1 (LOW)	5.7 (W26)	W28	Yes (14 days; recovered)	Dose reduction	0.5 mg/kg (W28-72+)
Placebo	2.7	6.1 (W26)	W28	Yes (13 days; recovered)	Dose reduction	0.5 mg/kg (W28-68+)
Placebo	2.0 (LOW)	5.2 (W26)	W28	Yes (104 days; recovered)	Dose reduction	0.5 mg/kg (W28-64+)
Placebo	1.9 (LOW)	4.9 (W34)	W36	No	None	None
Placebo	2.0 (LOW)	4.9 (W26)	W28	No	None	None
Placebo	2.3 (LOW)	4.6 (W46)	W48	No	None	None
Placebo	2.6	4.9 (W26)	W28	No	None	None
		4.7 (W34)	W36	Yes (15 days; recovered)	Dose reduction	0.5 mg/kg (W36-56+)
Placebo	2.5 (low)	4.7 (W34)	W36	No	None	None

"LOW" denotes values below reference range (< 2.5 mg/dL); for placebo subjects crossing over to burosumab after Placebo-controlled Treatment Period, Week 24 data are provided. If serum phosphorus >5.0 mg/dL at any time, unblind and dose reduce by half. If serum phosphorous >ULN (4.5 mg/dL) but ≤5.0 mg/dL, unblind and reduce dose by half if a second phosphorus result >ULN. "+" denotes continued dosing past cut-off date. The dose was reduced to 0.25 mg/kg at Weeks 20 and 24; however, the data entry system only allowed for recording of 2 digits. The dose was therefore recorded as 0.3 mg/kg. To be compliant with dose rounding rules, the dose was subsequently modified to 0.2 mg/kg at Week 28

In Study UX023-CL203, one subject (5%) had one serum phosphorus level above ULN. The dose was reduced but the event not reported as a TEAE.

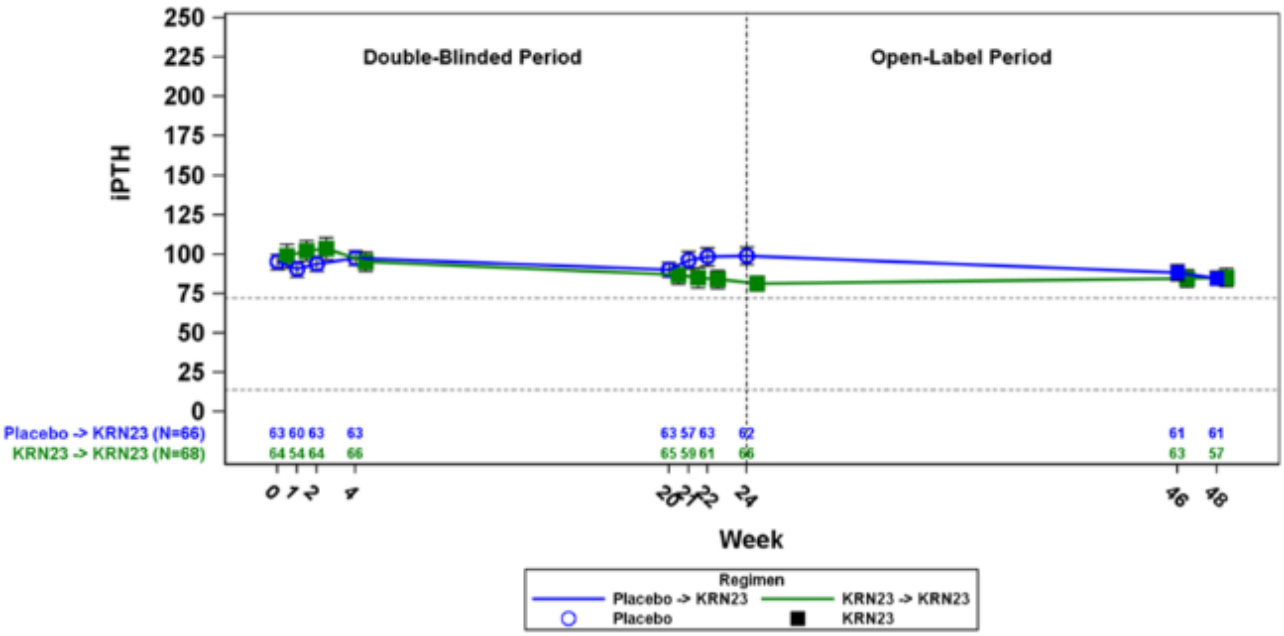
No subjects in Studies KRN23-INT-001 and KRN23-INT-002 or UX023-CL304 had elevations in serum phosphorus above ULN.

Overall, serum phosphorus elevations above ULN occurred in 18/176 (10.2%) adult subjects during burosumab treatment.

Intact Parathyroid Hormone

To be eligible for Study UX023-CL303, iPTH could not exceed ≥2.5 ULN. The mean iPTH concentration was above the ULN (>72 pg/mL) in both treatment groups at baseline. The mean ([standard error] SE) iPTH concentration was 98.9 (7.60) pg/mL (range: 23-447) in the burosumab group and 95.2 (4.89) pg/mL (range: 29-242) in the placebo group. The difference between groups (burosumab and placebo) in change from baseline to Week 24 was statistically significant (p = 0.0012).

Figure 34: iPTH (pg/mL) (Mean ±SE) and Change from Baseline (LS Mean ±SE): Study UX023-CL303 in ***Adult XLH*** *(Safety Analysis Set)*



Placebo subjects cross over to burosumab treatment at Week 24, and all subjects receive open-label burosumab after Week 24 in the Treatment Continuation Period.

Overall in the adult clinical development program, the subject incidence of TEAEs of increased serum iPTH in burosumab-treated adult subjects was 4.0%.

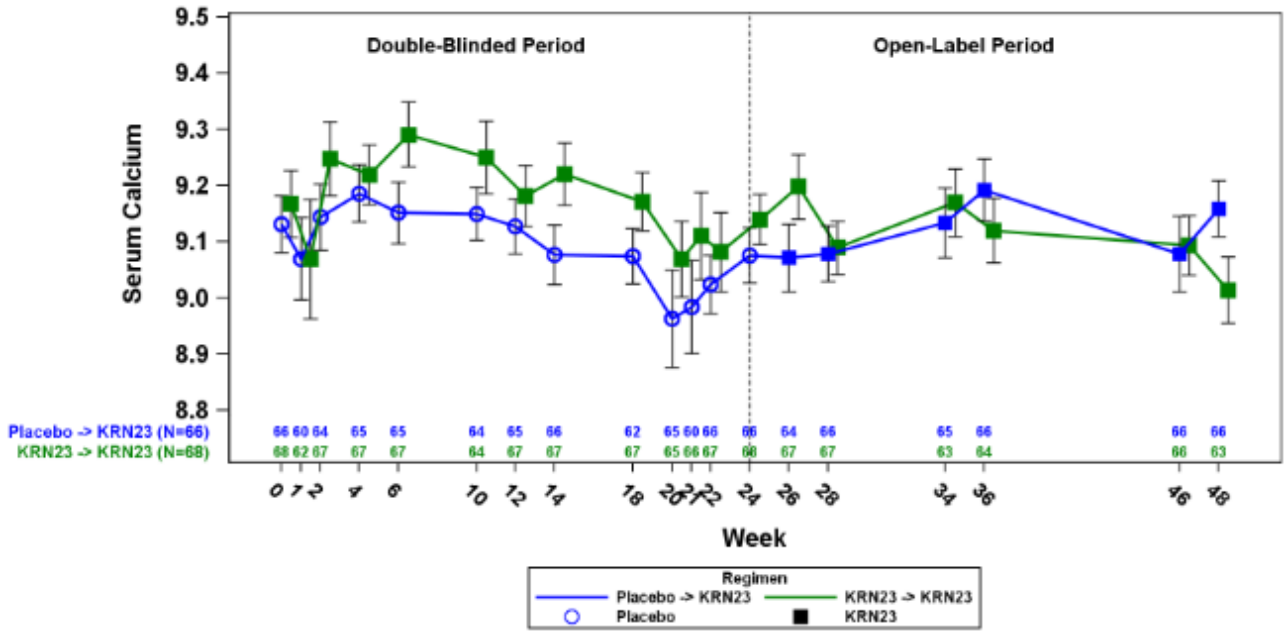
Considering the potential for hyperparathyroidism in subjects with XLH, the applicant was asked during the procedure to summarise all cases of hyperparathyroidism that have occurred in XLH subjects on burosumab treatment from the clinical development programme and post-marketing data in both adult and paediatric populations, including their relevant concomitant laboratory measurements and any clinical consequences. On review of the responses, there was 1 out of 116 paediatric patients with an AE of blood PTH increased and seventeen out of 176 adult subjects (9.7%) in the repeat dose burosumab XLH studies reported at least one adverse event of blood parathyroid hormone increased or hyperparathyroidism or hyperparathyroidism secondary. In the adult population, among the clinical trial cases, 11 out of the 15 adult subjects had elevated iPTH at study baseline and 1 paediatric subject had raised iPTH at screening visit. The majority of the TEAEs were related to transient or intermittent increases in parathyroid hormone levels above baseline values but were not accompanied by any clinically relevant changes in serumcalcium values or clinical signs and symptoms. No action was taken with the study medication as a result of the TEAEs.

Serum Calcium

In Study UX023-CL303, individuals with elevated serum calcium levels (≥10.8 mg/dL [2.7 mmol/L]) were excluded from the study.

At baseline and throughout the study, serum calcium levels generally remained within the normal reference range (8.6-10.2 mg/dL [2.1-2.5 mmol/L]). Changes from baseline are graphically presented in Figure 36.

*Figure 35: Serum Calcium Level (mg/dL) (Mean ±SE): Study UX023-CL303 in **Adult XLH** (Safety Analysis Set)*



Placebo subjects cross over to burosumab treatment at Week 24, and all subjects receive open-label burosumab after Week 24 in the Treatment Continuation Period.

TEAEs associated with *decreased blood calcium* were reported in 3 subjects in Study UX023-CL303 through the data cut-off date. Two of these events occurred during the Placebo-controlled Treatment Period, and included one subject in the burosumab group (serum calcium: 7.8 mg/dL [1.9 mmol/L]; event assessed as possibly related to study drug), and one subject in the placebo group, although the serum calcium levels in this subject were within the normal range (serum calcium: 8.7 mg/dL [2.2 mmol/L] [range: 8.6 – 10.2 mg/dL]; event assessed as probably not related to study drug). Study treatment was not disrupted in either subject. One subject had a TEAE of hypocalcaemia at Week 46 (serum calcium: 7.4 mg/dL [1.8 mmol/L]; event assessed as not related to study drug) which resolved after 16 days without treatment. The subject chose to discontinue after the Treatment Continuation period; the subject's last dose of burosumab was at Week 44, and the subject's last visit was Week 48.

No TEAEs associated with i*ncreased blood calcium* were reported through the data cut-off date.

Clinically meaningful changes in serum or urinary calcium were also not seen in Studies KRN23-INT-001 and KRN23-INT-002. In Study UX023-CL203, 1 subject reported a TEAE of hypercalciuria at Week 24, which was mild in severity and did not result in a change in burosumab treatment. The subject had had stable Grade 1 nephrocalcinosis at both Baseline and Week 24 and no nephrolithiasis.

Renal Function Laboratory Assessments

To be eligible for Study UX023-CL303, subjects were required to have an eGFR of ≥60 mL/min (or 45 to < 60 mL/min with confirmation that the renal insufficiency was not due to nephrocalcinosis).

Mean and median eGFR values for baseline, Week 24 and Week 48 in Study UX023-CL303 are summarised in Table 53.

*Table 51: Summary of eGFR UX023-CL303 **Adult XLH** Safety Analysis Set Week 48 Analysis (compiled from CSR by Assessor)*

Lab Test (Unit)	Visit		Placebo->KRN23 (N=66)	KRN23->KRN23 (N=68)	Total (N = 134)
eGFR (mL/min/1.73 m2)	Baseline	n	66	68	134
		Mean	117.0	114.5	115.7
		SD, SE	19.82, 2.44	19.46, 2.36	19.60, 1.69
		Median	119.5	116.0	117.0
		Q1, Q3	109.0, 129.0	103.5, 126.0	104.0, 129.0
		Min, Max	67, 153	67, 167	67, 167
eGFR (mL/min/1.73 m2)	Week 24	n	66	68	134
		Mean	119.0	114.1	116.5
		SD, SE	18.52, 2.28	17.66, 2.14	18.18, 1.57
		Median	121.0	115.0	117.5
		Q1, Q3	112.0, 130.0	103.0, 124.0	107.0, 126.0
		Min, Max	61, 152	73, 156	61, 156
eGFR (mL/min/1.73 m2)	Week 48	n	66	64	130
		Mean	118.0	116.1	117.1
		SD, SE	17.81, 2.19	19.21, 2.40	18.46, 1.62
		Median	122.0	117.0	119.5
		Q1, Q3	110.0, 130.0	106.0, 127.0	108.0, 130.0
		Min, Max	69, 150	75, 168	69, 168

One subject experienced a TEAE of decreased eGFR through the data cut-off date. The event occurred during the Placebo-controlled Treatment Period, was assessed as possibly related to study drug by the Investigator and did not disrupt study treatment.

A total of 8 adult subjects in Studies UX023-CL303, UX023-CL304 and UX023-CL203 with normal baseline serum creatinine results experienced a transient elevation in serum creatinine with subsequent normal values: 2 subjects enrolled in Study UX023-CL203 and 6 subjects enrolled in Study UX023-CL303 (4 while receiving burosumab; 2 while receiving placebo). Concurrent serum BUN levels were normal in 2 subjects receiving burosumab and mildly elevated in 6 subjects (2 placebo and 4 burosumab). These mild BUN elevations ranged from 24 to 32 mg/dL (reference range: 9-23 mg/dL) in subjects whose serum creatinine elevations were less than 1.1 × ULN and suggest mild dehydration as these were fasting blood samples. There were no TEAEs associated with serum creatinine levels through the data cut-off date.

One subject in the placebo arm experienced a TEAE of decreased eGFR through the data cut-off date. The event occurred at Week 12 during the double-blind period.

Serum Amylase

Several subjects entered Study UX023-CL303 with modest (Grade 1: 9% or Grade 2: 0.7%) serum amylase elevation. This has been observed previously in individuals with XLH in the burosumab development programme, without any apparent clinical consequences.

Shifts in serum amylase in the adult clinical development program are summarised in Table 54.

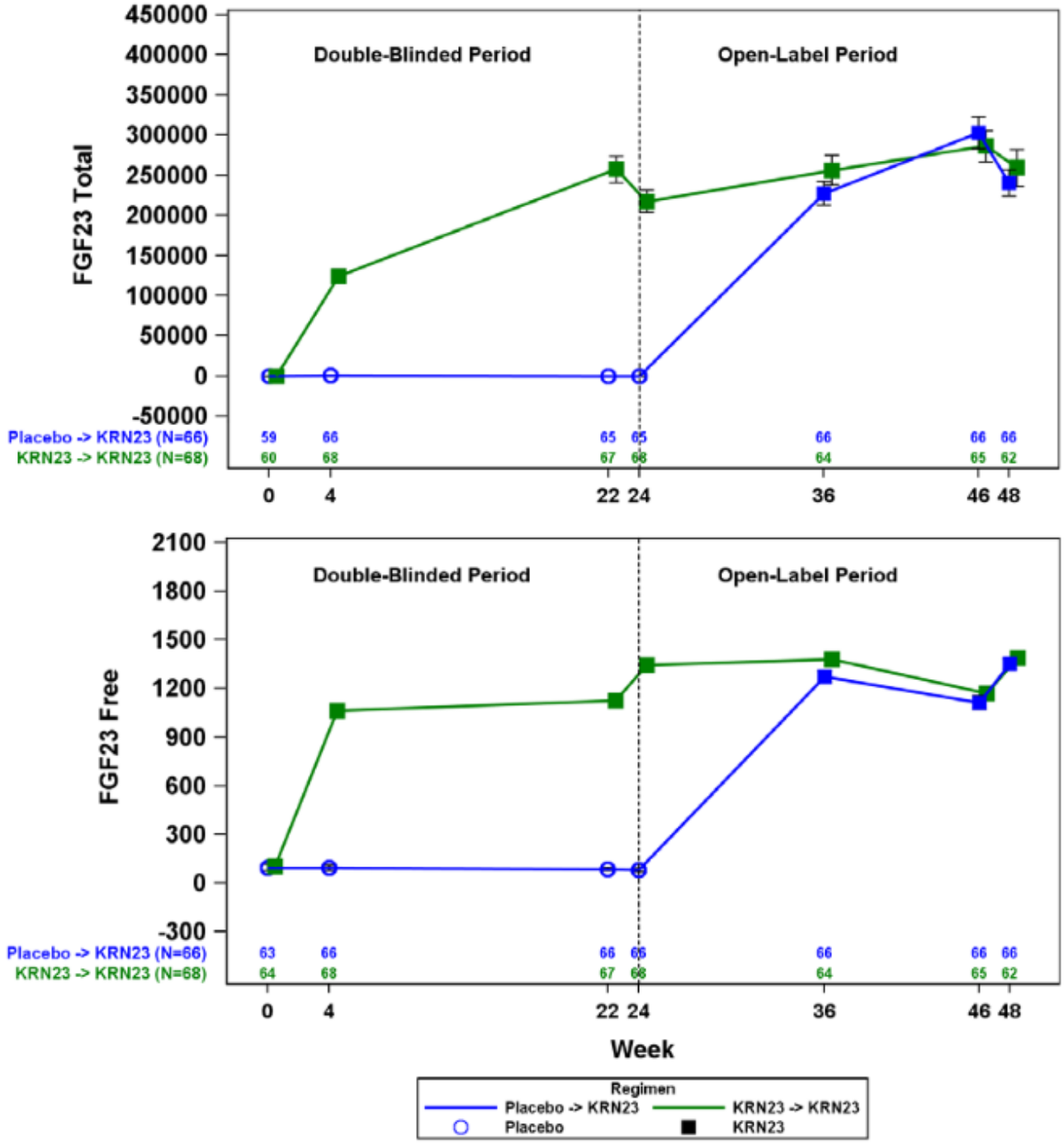
*Table 52: Shift Table – Serum Amylase Repeat Dose Studies – **Adult XLH** Safety Analysis Set*

			CL303 Double-Blind Period (Week 0-24)			CL304	CL203	INT-001/002*	
	Baseline Grade	Max Post-Baseline Grade	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	No Grade		57 (86.36%)	64 (94.12%)	121 (90.30%)	14 (100.00%)	19 (95.00%)	26 (92.86%)	161 (91.48%)
	1		8 (12.12%)	4 (5.88%)	12 (8.96%)	0	0	1 (3.57%)	13 (7.39%)
	2		1 (1.52%)	0	1 (0.75%)	0	0	0	1 (0.57%)
	3		0	0	0	0	1 (5.00%)	1 (3.57%)	1 (0.57%)
Post-Baseline	No Grade	2	0	0	0	0	1 (5.00%)	0	1 (0.57%)
	No Grade	1	1 (1.52%)	6 (8.82%)	16 (11.94%)	3 (21.43%)	5 (25.00%)	4 (14.29%)	26 (14.77%)
	No Grade	No Grade	56 (84.85%)	58 (85.29%)	105 (78.36%)	11 (78.57%)	13 (65.00%)	22 (78.57%)	134 (76.14%)
	1	2	1 (1.52%)	0	1 (0.75%)	0	0	0	1 (0.57%)
	1	1	5 (7.58%)	3 (4.41%)	9 (6.72%)	0	0	1 (3.57%)	10 (5.68%)
	1	No Grade	2 (3.03%)	1 (1.47%)	2 (1.49%)	0	0	0	2 (1.14%)
	2	3	0	0	1 (0.75%)	0	0	0	1 (0.57%)
	2	2	1 (1.52%)	0	0	0	0	0	0
	3	3	0	0	0	0	1 (5.00%)	1 (3.57%)	1 (0.57%)

FGF23

Serum levels of total and free FGF23 in Study UX023-CL303 are given in Figure 37.

Figure 36: FGF23 Levels (pg/mL) (Mean ± SE) (Safety Analysis Set)



Other Serum Chemistry

Clinically relevant changes in routine serum chemistry parameters were reported as TEAEs.

Vital Signs, Physical Findings, and Other Observations Related to Safety

No clinically meaningful changes from baseline were observed for vital signs in the paediatric studies. Results from the adult studies are summarised below.

ECG

Shifts in QTc intervals are summarised for all studies in adults with XLH in Table 55.

Table 53: Electrocardiogram QT Shift Table: Repeat-dose Studies in Adult XLH

			UX023-CL303			
			Double-blind Period (Week 0-24)		Total Burosumab [a] (N=134)	Overall Burosumab [b] (N=176)
	Baseline Category	Max Post-baseline Category	Placebo (N=66)	Burosumab (N=68)		
Baseline	≤450 msec		63 (95.45%)	67 (98.53%)	130 (97.01%)	169 (96.02%)
	>450-≤480 msec		1 (1.52%)	1 (1.47%)	2 (1.49%)	4 (2.27%)
	>480-≤500 msec		0 (0%)	0 (0%)	0 (0%)	1 (0.57%)
	Missing		2 (3.03%)	0 (0%)	2 (1.49%)	2 (1.14%)
Post-baseline	≤450 msec	>450-≤480 msec	0 (0%)	0 (0%)	3 (2.24%)	5 (2.84%)
	≤450 msec	≤450 msec	3 (4.55%)	1 (1.47%)	126 (94.03%)	163 (92.61%)
	≤450 msec	Missing	60 (90.91%)	66 (97.06%)	1 (0.75%)	1 (0.57%)
	>450-≤480 msec	>480-≤500 msec	0 (0%)	0 (0%)	0 (0%)	1 (0.57%)
	>450-≤480 msec	>450-≤480 msec	0 (0%)	0 (0%)	1 (0.75%)	1 (0.57%)
	>450-≤480 msec	≤450 msec	0 (0%)	0 (0%)	1 (0.75%)	2 (1.14%)
	>450-≤480 msec	Missing	1 (1.52%)	1 (1.47%)	0 (0%)	0 (0%)
	>480-≤500 msec	>450-≤480 msec	0 (0%)	0 (0%)	0 (0%)	1 (0.57%)
	>480-≤500 msec	≤450 msec	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Missing	≤450 msec	0 (0%)	0 (0%)	2 (1.49%)	2 (1.14%)
	Missing	Missing	2 (3.03%)	0 (0%)	0 (0%)	0 (0%)
Post-baseline	≤450 msec	>30-≤60 msec	0 (0%)	0 (0%)	3 (2.24%)	8 (4.55%)
	≤450 msec	≤30 msec	3 (4.55%)	1 (1.47%)	126 (94.03%)	160 (90.91%)
	≤450 msec	Missing	60 (90.91%)	66 (97.06%)	1 (0.75%)	1 (0.57%)
	>450-≤480 msec	>30-≤60 msec	0 (0%)	0 (0%)	0 (0%)	1 (0.57%)
	>450-≤480 msec	≤30 msec	0 (0%)	0 (0%)	2 (1.49%)	3 (1.70%)
	>450-≤480 msec	Missing	1 (1.52%)	1 (1.47%)	0 (0%)	0 (0%)
	>480-≤500 msec	≤30 msec	0 (0%)	0 (0%)	0 (0%)	1 (0.57%)
	Missing	Missing	2 (3.03%)	0 (0%)	2 (1.49%)	2 (1.14%)

Note: QTcF was used for summary.

Nine subjects (5.1%) had maximum QTcF interval changes from baseline of >30 msec and ≤60 msec; no cardiac TEAEs were reported in these subjects.

One subject (placebo) entered the study with an abnormal ECG considered potentially clinically relevant; the subject's medical history included heart palpitations due to or caused by Wolff-Parkinson-White Syndrome. Following radiofrequency heart ablation on Study Day 332, this subject's ECG showed normal sinus rhythm at Week 48. Another subject (placebo) had an abnormal ECG interpreted as potentially clinically relevant at Week 24; no cardiac TEAEs were reported for this subject through the data cut-off date.

Heart rate and blood pressure

Clinically relevant changes in vital signs were reported as TEAEs.
Through the data cut-off date across all adult repeat-dose studies, increased blood pressure or hypertension was reported in 13 subjects, 3 while receiving placebo and 10 while receiving burosumab. None of the events were considered serious or attributed to study drug. Of the 10 subjects receiving burosumab, 2 subjects had a documented history of hypertension. No trends in blood pressure or heart rate were observed; subjects were just as likely to have elevations in blood pressure or heart rate on 3 consecutive visits as they were to have decreases in these measurements across all adult studies (Table 56).

Table 54: Summary of Vital Signs Outliers: Repeat-dose Studies in Adult XLH

	UX023-CL303			
	Double-blind Period (Week 0-24)		Total Burosumab[a] (N = 134)	Overall Burosumab[b] (N = 176)
	Placebo (N = 66)	Burosumab (N = 68)		
Increase from BL of ≥15 mmHg for 3 consecutive visits in SBP				
Subject Incidence - n (%)	0 (0%)	0 (0%)	3 (2.24%)	15 (8.52%)
Event Incidence	0	0	3	34
Increase from BL of ≥10 mmHg for 3 consecutive visits in DBP				
Subject Incidence - n (%)	0 (0%)	0 (0%)	7 (5.22%)	22 (12.50%)
Event Incidence	0	0	7	81
Increase from BL of ≥15 beats/minute for 3 consecutive visits in HR				
Subject Incidence - n (%)	0 (0%)	0 (0%)	2 (1.49%)	10 (5.68%)
Event Incidence	0	0	2	35
Decrease from BL of ≥15 mmHg for 3 consecutive visits in SBP				
Subject Incidence - n (%)	0 (0%)	0 (0%)	6 (4.48%)	18 (10.23%)
Event Incidence	0	0	6	55
Decrease from BL of ≥10 mmHg for 3 consecutive visits in DBP				
Subject Incidence - n (%)	0 (0%)	0 (0%)	4 (2.99%)	17 (9.66%)
Event Incidence	0	0	4	60
Decrease from BL of ≥15 beats/minute for 3 consecutive visits in HR				
Subject Incidence - n (%)	0 (0%)	0 (0%)	2 (1.49%)	5 (2.84%)
Event Incidence	0	0	2	18

Weight and height

There has been interest in the role that FGF23 and hypophosphataemia play in fat deposition and body weight in patients with XLH. The high incidence of above normal BMI has been seen in children with XLH and the incidence increases with age (Zhoukouskaya et al, 2019). It has been proposed that altered thermogenesis as a result of low phosphate affecting ATP availability and central control of satiety may be a contributory factor. Although there are no long-term data yet that show an effect of burosumab on BMI

or fat metabolism, the correction of serum phosphate and improved exercise tolerance are an additional benefit in this complex disease.

Study UX023-CL303 (approximately 40% of subjects were ≤35 years) showed that subjects had significant comorbidities at study entry (e.g., obesity and hypertension), which are likely associated with the impact of XLH on mobility and physical function and could be prevented or alleviated by continued burosumab treatment from the adolescent years to adulthood. For instance, 75% of subjects (100/134) in Study UX023-CL303 were classified as either overweight, obese or severely obese at study entry, which is likely related to the impact of XLH on their ability to participate in physical activities.

Other Observations Related to Safety: Spinal Surgery

Spinal stenosis, which often can progress to significant spinal cord compression, is a well-described phenomenon in patients with XLH (Soehle, 2002).

At least 30 patients with XLH (including some with vitamin D-resistant hypophosphataemia prior to the discovery of the molecular genetic basis of XLH) have been described in the literature to have cord compression (Soehle, 2002), (Velan, 2001), (Kawaguchi, 2009), (Xie, 2014), (Shiba, 2015), (Watts, 2015), (Riccio, 2016), (Chesher, 2018). Spinal stenosis occurs at multiple anatomical levels of the spine in XLH and due to multifactorial causes, making it challenging to unify into a common pathophysiology. A subset of cases can be associated with ossification of either the posterior longitudinal ligament or the ligamentum flavum. Additionally, whether it can be associated with conventional therapy with phosphate and active vitamin D metabolites/analogues is unclear, as some cases in the literature occurred with no therapy or minimal therapy, implying that it may be secondary to the XLH disease process itself.

In Study UX023-CL303, a total of 27 subjects (20.1%) had a medical history at baseline of either spinal stenosis, cord compression, or another event term likely to be related to either spinal stenosis or cord compression.

Across all repeat-dose adult studies, a total of 6 subjects had spinal surgery, including 1 subject each from Studies KRN23-INT-001/KRN23-INT-002 and UX023-CL304, and 4 subjects from Study UX023-CL303 (2 in the burosumab group and 1 each in the placebo→burosumab group and the placebo group).

The 6 cases of spinal surgery with pre-existing stenosis (or a longstanding history of back pain) seem consistent with the natural history of the disease and with the cases reported in the medical literature (including assessment by age, anatomical region, and anatomical cause). The medical review of these cases demonstrated that for 3 of these cases there was either no evidence of clinical progression of spinal stenosis while on study (2 subjects) or alternatively that it began while the subject was on placebo (1 subject). For 2 of these 3 cases, surgery had also either been pre-planned or previously discussed. One subject had an extensive history of prior spinal surgery and one subject had an extensive history of back issues, including back surgery and one subject had a longstanding history of back pain.

The MAH concludes that given the relatively frequent occurrence of spinal stenosis and cord compression in XLH, the difficulty in unifying the different anatomical causes of spinal stenosis in XLH (and in these individual cases) into a common pathophysiology, and the medical review findings of these cases, the data suggest that the number of spinal surgery cases seen in the study are not unexpected and are unlikely to be related to burosumab treatment. Burosumab's mechanism of action and the lack of meaningful changes of measures of ectopic mineralisation suggest that burosumab is unlikely to have worsened the condition of spinal stenosis, and that, most likely, the sequelae experienced by these subjects were natural progression of the condition itself.

Safety in special populations

Intrinsic Factors

As safety data in subjects >65 years of age were limited (no subject >66 years of age was included in the studies), no meaningful conclusions can be drawn for this population.

Review of safety data by sex in both paediatric and adult subjects revealed no meaningful differences.

As burosumab dose is calculated on a mg/kg basis, a subject's weight should not be a factor; a minimum dose of 10 mg and a maximum dose of 90 mg, regardless of weight, is proposed in the product information.

Data were limited in a number of intrinsic factors such as race and baseline history of hepatic/renal impairment. As the preponderance of the subjects were white/Caucasian, meaningful conclusions by race/ethnicity could not be drawn. Subjects with a history of liver impairment were not excluded from burosumab clinical trials; however, the data on the effect of burosumab in subjects with liver impairment are also limited. Subjects with severe kidney impairment were excluded from clinical trials, as they could be prone to increases in serum phosphorus and calcium; as such, data on the effect of burosumab in subjects with renal impairment are limited.

Use in Pregnancy and Lactation

Currently, very limited data are available for the use of burosumab in pregnant women.

Through the data cut-off date, 3 pregnancies have been reported in 3 female subjects enrolled in clinical studies with burosumab. In addition, a pregnancy was reported in the partner of a male subject. All 4 women delivered healthy infants at term. Short summaries of the cases are given below:

- In the first case, the woman had a positive pregnancy test 54 days post last dose of burosumab. No further burosumab was given during pregnancy. To episodes of spotting/cramping were reported during pregnancy.
- In the second case, conception date was approximated to Study Day 422. The last dose of study drug was received on Study Day 423, and subsequently, study treatment was discontinued as per protocol. No complications were reported.
- In the third case, conception date was approximated to Study Day 326. The last dose of study drug was received on Study Day 336. On Study Day 345, urine pregnancy test was positive and subsequently, study treatment was discontinued as per protocol. No complications were reported.
- In the fourth case, the father received the most recent dose of burosumab (90 mg) prior to his partner becoming pregnant at Study Week 68. No information was given on the approximate day of conception in relation to this dose. Induction of labour was planned due to suspected macrosomia. Dilation arrested at 7 cm, and the mother underwent a primary low transverse caesarean delivery 6 days before the expected due date.

Adolescents

Phase 2 Study UX023-CL201 recruited children up to the age of 12 years and patients were recruited at the upper end of the age inclusion criteria. Study UX023-CL201 followed subjects for up to 160 weeks; these final safety data are available and are included in this variation. Specifically, 11 subjects (all female) were identified whose growth plates closed during the course of the study. For one of the eleven subjects, the last reading with open growth plates was the Week 64 reading. The remaining ten subjects had open growth plates at the Week 88 reading. The mean age of these subjects was 9.8 years on study entry (range 8-11 years) and all subjects had received previous treatment with oral phosphate and

vitamin D (mean duration of treatment 8 years). At Week 160, the mean burosumab dose was 1.06 mg/kg (range 0.5-1.8 mg/kg) Q2W. All subjects experienced at least 1 TEAE and 8 experienced related TEAEs; all reported TEAEs were non-serious. Review of the individual safety data for these subjects and the summarised data did not reveal any differences in their safety profile compared to the overall study population. In particular, there was no suggestion that longer term treatment resulted in more frequent AEs or of AEs of a different nature.

Currently, burosumab is approved in the EU for the treatment of all children up to the age of 18 years, except those without "growing skeletons". Burosumab has been commercially available in the US since 17 Apr 2018 for the treatment of children with XLH aged 1 year and older. Over this time, there have been no safety signals that would raise concern over treating adolescents who have reached maximum vertical height and/or with closed long bone growth plates. In addition, a small group of adolescent patients (N = 132) have been started burosumab treatment in a UK, through an expanded access programme, with no reports of treatment being poorly tolerated or stopping (Dharmaraj et al, 2019).

Safety related to drug-drug interactions and other interactions

No drug interaction studies have been conducted with burosumab.

Discontinuation due to adverse events

Three subjects in the adult development program discontinued study drug because of a TEAE; one in Study KRN23-INT-001 and two in Study KRN23-INT-002. Two of the subjects later entered extension study UX023-CL203:

- A subject in KRN23-INT-001 experienced a TEAE of injection site urticaria on Study Day 57. The subject was discontinued from the study due to the event. The Investigator considered the event to be moderate in intensity and probably related to study drug.
- A subject with a medical history of nephrocalcinosis/nephrolithiasis experienced a TEAE of haematuria with painful urination on Study Day 4. Study medication was discontinued after the first dose due to the events of haematuria, painful urination, and kidney stones. All three TEAEs were considered by the Investigator to be possibly related to the study drug. The subject subsequently enrolled in Study UX023-CL203 approximately 3 years later. Forty-two weeks after initiating treatment on this study, the subject experienced a TEAE of nephrolithiasis. The event was mild in severity and deemed unrelated to study treatment by the Investigator. Burosumab was not changed in response to the event and subject remains on study as of the data cut-off date.
- A subject with a medical history of RLS experienced an AE of moderate increase in RLS symptoms two weeks after their final dose of burosumab on Study KRN23-INT-001 and 43 days before KRN23-INT-002 Study Day 1. On Study Day 135, the subject experienced severe worsening of RLS with right arm involvement and the study drug was discontinued. The subject subsequently enrolled in Study UX023-CL203 approximately 2.5 years later. The subject did not report a recurrence of worsening of RLS after more than 48 weeks of treatment and remains on the study.

Post-marketing experience

Data presented in the most recent PSUR submitted in the EU for burosumab showed that cumulatively up to 31 Jan 2019, a total of 1,224 patients have been exposed to commercially available burosumab or in early access programmes. A review of the collated post-marketing safety data did not show any changes

in the benefit-risk profile of burosumab. Overall, the reported AEs were either expected adverse drug reactions for burosumab or were due to the patients' underlying medical condition under treatment.

2.5.1. Discussion on clinical safety

The adult safety database comprises of 176 subjects having received at least one dose of burosumab in studies KRN23-INT-001/KRN23-INT-002, UX023-CL203, UX023-CL303 and UX023-CL304. The total cumulative exposure is 205 patient-years and the mean duration of exposure was 61 weeks.

96-100% of the subjects in the five studies were reported with a treatment emergent adverse event (TEAE), of which 55-64% were deemed as related to burosumab.

The rates of reported TEAEs were comparable in both treatment arms during the placebo-controlled period of UX023-CL303 (94% in the burosumab arm and 92% in the placebo arm), whereas somewhat more TEAEs were deemed as treatment related in the burosumab arm (44% vs 39%). Two subjects (3%) in each treatment arm were reported with an SAE. No SAE was deemed as related to the study drug in UX023-CL303.

TEAEs were generally less common in adults than in the paediatric population and the distribution of TEAEs between SOCs differed between the adult and paediatric population, but no new and unexpected TEAEs were reported in the adult population compared to the paediatric population.
In the adult safety database, TEAEs were most frequently reported in the SOCs Infections and infestations (68%), Musculoskeletal and connective tissue disorders (64%), Nervous system disorders (49%), General disorders and administration site conditions (48%) and Gastrointestinal disorders (46%).

With some exceptions described below, the frequency of reported TEAEs in each SOC was balanced between the two treatment arms of study UX023-CL303. TEAEs more common in the burosumab arm included back pain (14% vs 6% for burosumab and placebo, respectively), Tooth abscess (13% vs 8%), restless legs (RLS; 12% vs 8%) Vitamin D decreased (12% vs 5%), dizziness (10% vs 6%), constipation (9% vs 0%), and investigation (21% vs 14%).

Headache and tooth abscess/tooth infections were more common in the burosumab arm also in the paediatric active controlled open-label study UX23-CL301 (provided in procedure II/04). Both items are labelled ADRs for the paediatric population and are included in the PI also for the adult population; so is Vitamin-D decreased. In procedure II/04, the SmPC for the paediatric population was amended to include information regarding the fact that substitution with inactive vitamin D may be needed. The MAH has agreed that the same information should apply also for the adult population. Back pain is included in the PI for adults with XLH. RLS is assigned an AESI for Crysvita and is further discussed below. No individual Preferred Terms within the SOC Investigations had a frequency of ≥5%, i.e. approximately 3 subjects in either treatment arm.

In summary, TEAEs were generally more common among children and the distribution of TEAEs between SOCs differed between the adult and paediatric population, but no new and unexpected TEAEs were reported in the adult population compared to the paediatric population.

Subjects with severe kidney impairment were excluded from clinical trials, and the lowest baseline eGFR in Study UX023-CL303 was 67 ml/min/1.73 m2. Subjects with a history of liver impairment were not excluded from burosumab clinical trials; however, the data on the effect of burosumab in subjects with liver impairment are also limited. Upon request, the MAH has performed analyses on the subgroups of the population with impaired liver and kidney impairment.

In the adult repeat dose XLH studies, 55 out of a total of 176 subjects (31.3%) were found to have either a history of hepatobiliary disorder of any kind (n=16) and/or impairment in liver function tests (any value

above upper limit of the normal range) (n=44) at baseline ("liver cohort"). The most common hepatobiliary disorder was hepatic steatosis (n=7), followed by cholelithiasis (n=5) and cholecystitis (n=2). Due to a low number of events, direct comparisons to the total study population is difficult, but there were no new safety concerns identified in the 55 subjects in the liver cohort. All 55 subjects reported at least one treatment-emergent adverse event (TEAE) compared to 173/176 (98%) in the overall burosumab population. A slightly higher number of subjects in the liver cohort reported a serious AE (SAE) (22% vs 16% in the overall population); however, none of these events in the liver cohort were considered related to burosumab. Of note, 8 of the 55 subjects (14%) in the liver cohort had TEAEs of abnormal liver function or hepatobiliary disorders, whilst 2 of 122 (2%) without liver impairment at baseline had TEAEs of abnormal liver function or hepatobiliary disorders. It is agreed with the Applicant that it is to be expected that any individual with underlying hepatic disorder or conditions predisposing to hepatic disease could be more likely to experience hepatic related events, in the absence of health intervention intended to treat existing hepatic function abnormalities. The Applicant should continue to monitor for hepatic related safety signals in burosumab treated patients as part of routine PV monitoring.

Only 13 of the patients in Study UX023-CL303 had an eGFR <90mL/min/1.7m2, all with an eGFR >60mL/min/1.7m2, i.e. CKD2. From the limited data, there is no clear evidence of a difference in safety profile for these patients when treated with burosumab. However, the SmPC appropriately states that "Burosumab has not been studied in renal impairment" and there is a contraindication for severe renal impairment or ESRD. No further actions are considered warranted.

There were no fatal events through the data cut-off date in any of the studies; and the one fatality reported after the data cut-off in UX023-CL303 was clearly unrelated.

Before data cut-off, SAEs were reported in a total of 28 subjects on burosumab treatment and two on placebo treatment in the safety database. In total, one SAE was assessed as possibly related to study treatment (one event of angioedema in UX023-CL203). In this case, a woman on treatment with both lisinopril and burosumab developed a life-threatening event of angioedema, assessed as possibly related to both drugs by the Investigator. It is however agreed with the MAH that, as the subject continued on study medication without rechallenge hypersensitivity reactions after discontinuation of lisinopril, a causal association to lisinopril is more likely.

In Study UX023-CL303, there was a somewhat higher number of SAEs in the burosumab→burosumab group Week 24-48 (n=5) compared to Week 0-24 (n=2) which raises the question as to the potential for increased adverse events with prolonged duration of treatment with burosumab. Upon request, the MAH has presented exposure adjusted event incidence for SAEs/year for the individual studies and then for total treated burosumab patients, all of which are low ranging from 0.004- 0.062.

Among the 28 subjects reporting a SAE during burosumab treatment, four subjects reported malignancies (lung adenocarcinoma in a non-smoker subject, colon carcinoma in a subject with positive family history of genetic mutations for BRCA2 and MSH2, chordoma in a subject and a case of breast cancer in a female subject). None of these events were assessed as related. No further actions are therefore considered warranted at this time point. Nonetheless, the malignant chordoma is notable, as such malignancies are very rare. A single event like this is considered a coincidence, but should additional events be reported, this must be investigated in depth. At this time point, however, no additional reports on chordoma in a clinical study or as a post-marketing events have been retrieved.

Three subjects in the adult safety database discontinued study drug because of a TEAE; one in Study KRN23-INT-001 (urticaria) and two in Study KRN23-INT-002 (nephrolithiasis; restless legs). The two subjects discontinuing KRN23-INT-002 later entered extension study UX023-CL203 without recurrence of the event through data cut-off.

Adverse events of special interest (AESI) for Crysvita is Injection site reactions (IRS), Hypersensitivity, Hyperphosphataemia, Ectopic mineralisation, Restless legs (RLS) and Anti-burosumab antibodies (ADA).

A lower incidence of ISR was reported in the adult (25%) compared to the paediatric population (58%). This is not entirely unexpected as the majority of the subjects in the paediatric clinical development program received burosumab every second week (Q2W), whereas the adult subjects were treated Q4W. The incidence of ISR was similar in the treatment arms during the placebo-controlled period of study UX023-CL303 (12% in each arm).

Similarly, the difference in hypersensitivity TEAEs between the paediatric and adult populations (43% vs 19%, respectively) may at least in part be explained by the difference in administration frequency. The only severe hypersensitivity event reported in the adult safety database was the event of angioedema discussed above.

Hyperphosphataemia in adults was defined as serum phosphorus >4.5 mg/dL [>1.45 mmol/L]. In total, nine hyperphosphataemia TEAEs in eight subjects were reported in the adult studies, all in UX023-CL303. 5/8 subjects with hyperphosphataemia required protocol-specified dose reductions.
The selection of hyperphosphataemia episodes to be reported as hyperphosphataemia TEAE is not fully understood. 18/174 subjects (10%) in the adult safety database were reported with serum phosphorus levels above ULN at least at one occasion. In eleven of these eighteen subjects, the dose was reduced. Of those, nine events were reported as TEAE, whereas the remaining two, one subject each in UX023-CL303 and UX023-CL203, were not.
Seventeen of the totally eighteen subjects reporting hyperphosphataemia in the adult safety data base were enrolled in UX023-CL303. All events were reported during treatment with burosumab, either during the placebo-controlled period (N=9) or after switch to burosumab in the open-label phase (N=8), most often in the beginning of treatment.
Hyperphosphataemia was not reported in any subject in the paediatric safety database at MAA. Due to the mechanism of action, hyperphosphataemia was not an unexpected finding but an anticipated event already reflected in SmPC sections 4.2 and 4.4. Furthermore, the MAH proposes to amend SmPC section 4.8 for the adult population to include hyperphosphataemia, which is endorsed. However, it should be kept in mind that hyperphosphataemia may reflect over-suppression of FGF23.

In the procedure leading to the conditional MA for the paediatric population, the timing of blood testing was extensively discussed. Blood tests were obtained fasting, before study drug was administered, and so do not display the peak phosphate concentration as serum phosphate concentration fluctuates / rises in response to dietary intake. In the initial MAA, testing of post-prandial phosphate levels was requested as substudies in both children (UX023-CL301) and adults (UX023-CL303). The MAH has provided a summary of data from both studies. The paediatric substudy consisted of 13 children >3 years of age, including 10 subjects from the burosumab→burosumab group and 3 subjects from the active control→burosumab group. The adult substudy included 26 subjects; 13 each from the burosumab→burosumab group and the active control→burosumab group. In both studies, all subjects fasted for ≥8 hours prior to breakfast. In both substudies, blood samples for determination of serum phosphate were collected before breakfast and 1 and 2 hours after the completion of the meal. In the adult substudy, samples were also collected before lunch and 1 and 2 hours thereafter. Burosumab treatment did not cause post-prandial excursions above the age adjusted upper limits of normal in serum phosphorus or serum calcium in any subject in either substudy.

Assessment of ectopic mineralisation in the kidney is not entirely straight forward, as on the one hand, nephrocalcinosis/nephrolithiasis are features of XLH, but on the other hand, there is a risk of increased ectopic mineralisation due to an increase in urine calcium with burosumab treatment. However, in this limited material, there are no indications of an accelerated ectopic renal mineralisation by burosumab. The rate of nephrocalcinosis/nephrolithiasis TEAEs during the 24 Week placebo-controlled period were

comparable between the treatment arms (four events in the placebo arm versus three events in the burosumab arm) and there were no meaningful changes in shift in nephrocalcinosis score from baseline between the treatment arms during the same period.
Cardiac ectopic mineralisation was assessed by ECHO. Of note, during the paediatric clinical studies, cardiac CT was also performed to detect ectopic mineralisation. The use of ECHO in monitoring for ectopic calcification was performed in line with clinical practice and thus accepted. The MAH was asked to discuss whether potential cardiac mineralisation should be monitored during treatment. The MAH has responded that no clinically meaningful changes from baseline or differences between treatment groups in any ECHO parameter were observed throughout these studies in adult XLH patients and that no cardiac safety signal was observed in paediatric XLH patients is accepted. Similarly, no cardiac signal has emerged in PSURs. Monitoring of biochemical parameters, such as serum phosphate, alone is therefore agreed.

The exact mechanism of RLS in XLH subjects treated with burosumab is not known. It is hypothesised that increasing serum phosphorus levels near/into the normal range in subjects that have been chronically and severely hypophosphataemic may precipitate RLS symptoms/severity. The incidence of RLS was higher in the burosumab versus the placebo treatment arm during the double-blind period of study UX023-CL303 (12% vs 8%), indicating that a causal association is possible.

20/134 (15%) of the subjects in UX023-CL303 had pre-existing ADA. Three of those had previously been treated with burosumab in another study. 7/20 subjects were ADA negative after baseline and none of the 13/20 continuously ADA positive subjects had an increase in antibody titre during treatment.
Eight subjects were reported with treatment emergent ADA. These subjects had transient immune responses, with ADA-positive samples at only 1 or 2 post-treatment time points. No neutralising activity was detected in any of the ADA-positive subjects.

To study the impact ADA on efficacy, the MAH has reviewed the serum phosphorus levels at Week 22 and Week 46 (peak effect) and Week 24 and Week 48 (trough value) in ADA-positive subjects compared to the overall population. For the four subjects with treatment-emergent antibodies in the burosumab arm, there was a trend towards a smaller mean change from baseline compared to the overall population (+0.78 versus +0.88 mg/dL, respectively, at Week 22 and +0.58 versus +0.94 mg/dL arm at Week 46). For the four subjects in the placebo arm, on the other hand, there was no such trend (+0.20 versus +0.10 mg/dL, respectively, at Week 22 and +1.33 versus +1.11 mg/dL arm at Week 46).
To study the impact ADA on safety, the MAH has reviewed events of injection site reactions and hypersensitivity in 28 subjects positive for ADA at Baseline or any postbaseline visit in Study UX023-CL303. 20/28 did not have burosumab-emergent ISRs or AEs of hypersensitivity, 5/28 had an ISR and 3/28 reported at least one hypersensitivity AE. In all cases, the events resolved without discontinuation of the study drug. Events of ISRs and/or hypersensitivity were not necessarily coincident with the timing of samples testing positive for ADA, and no correlation between the occurrence of ISR, hypersensitivity AEs, and ADA was evident.
The MAH was asked to present the occurrence of TEAEs of injection site reactions (ISRs) and hypersensitivity for patients who were ADA positive and ADA negative for both adult and paediatric populations. Most of the patients reporting such TEAEs were ADA negative. There did not appear to be any pattern to differences in occurrences e.g. grade of the adverse event based on ADA status. It is agreed that there is no evidence from the presented data that immunogenicity has an impact on TEAEs of ISRs or hypersensitivity AEs. No new information on ADA has emerged after the data base lock for the MAA.

Long-term data in the adult population is still scarce. Overall, in the data provided, there were no new safety concerns or any relevant differences in safety profile with burosumab treatment beyond 6 or 12 months compared to the first 6 months. 65 subjects received burosumab for more than 2 years. The safety profile of these subjects did not reveal any differences in the nature of the TEAEs compared to the overall safety profile of burosumab. The MAH has proposed to include adult patients in the PASS. The two

ongoing studies, DMP and SUNFLOWER, should also provide further safety information. The MAH's commitment to include other safety reports within PSURs is endorsed.

No new and unexpected laboratory findings or impact on vital signs were identified in the adult database.

Considering the potential for hyperparathyroidism in subjects with XLH, the MAH was asked to summarise all cases of hyperparathyroidism in the clinical development program. The overall analyses of all the TEAEs of hyperparathyroidism reflected mostly transient or intermittent changes in iPTH and no relevant clinical consequences were associated with these changes in laboratory results. Such transient changes were seen also for patients on placebo treatment. According to the MAH, there was a downward trend for iPTH concentrations for adult patients treated with burosumab compared to placebo. This will need further study before any definitive conclusions could be drawn in this regard. However, overall it is agreed that TEAEs of hyperparathyroidism that did occur in adult and paediatric clinical trials and also from post-marketing data of burosumab were relatively low and in most cases did not lead to treatment discontinuation.

At the time of the initial MAA, concerns were raised about the issue of elevated free FGF23 in serum. The applicant explained that the apparent increase in serum [free FGF-23] was an artefact of the assay system and that the presence of free FGF23 was believed to be minimal. The MAH has verified that the same assay was used in the adult studies. Moreover, at the time of the MAA, the MAH demonstrated that burosumab is expected to fully inhibit FGF23 following administration. Specifically, with 1mg/kg Q4W in particular in adult patients full FGF23 binding is expected over most of the dosing interval with only ~0.1% unbound FGF23 at the end of the dosing interval.

At study entry, most patients in XLH clinical development programme were overweight or obese and below average height. Only eight subjects had follow-up height measurement up to week 168; however, as Study UX023-CL303 was an adult population, no impact on height is expected. There was a trend towards a larger number of subjects in the burosumab treatment arm with weight decrease at Week 24 versus placebo, whereas the number of subjects with weight increase tended to be larger in the placebo arm. However, both placebo- and burosumab-treated subjects showed fluctuations in weight and no definitive conclusions can be drawn.

No new or unexpected post-marketing events are reported in PSURs submitted to the EMA or Periodic Adverse Drug Experience Report submitted to the FDA.

Assessment of paediatric data on clinical safety

Crysvita has a conditional MAA for treatment of children with XLH from the age of one year and adolescents with growing skeletons. No children were included in the studies forming the adult clinical development program assessed in this report.

Adolescents with closed epiphyseal growth plates have not been included in any clinical studies, neither in the paediatric nor the adult development program. In paediatric Study UX023-CL201, there were 11 adolescent subjects identified whose growth plates closed during the course of the study. For one of the eleven subjects, the last reading with open growth plates was the Week 64 reading. The remaining ten subjects had open growth plates at the Week 88 reading. No information on safety in adolescents with closed epiphyseal growth plates is considered to be available from this limited group. Upon request, the MAH presented a summary of all available data on adolescents aged 12-18 years treated with burosumab. Available Data from adolescent subjects treated with burosumab Q2W dosing regimen demonstrates similar efficacy and safety profiles to the paediatric population from the Study UX023-CL201 and two interim reports for Study KRN23-003 and KRN23-004.
Thus, the safety profile in adolescents with closed epiphyseal growth plates needs to be extrapolated from

the paediatric and adult subpopulations. The safety profile in the paediatric and adult population are similar with a few exceptions, e.g. hyperphosphataemia and restless legs. There are no reasons to suspect that the safety profile with burosumab treatment would differ in any meaningful way in this specific population compared to younger children or adults, given that the exposure is comparable.

The MAH anticipates that data in adolescents will be generated by four planned or ongoing studies: the UK early access program (EAP), the UX023-CL401 X-Linked Hypophosphatemia Disease Monitoring Program (DMP), the Sunflower Study and the European Registry Study (2018-16-EU-BUR). Updates on the study status and safety data will be provided through routine PSURs and study reports will be submitted to the Agency as they become available. In their response, the MAH notifies that data from the UK EAP (n=132) includes a smaller group of adolescents than previously stated although the exact number has not been provided.

2.5.2. Conclusions on clinical safety

The safety profile in the adult safety database is in line with the known safety profile for Crysvita in the paediatric population. No new and unexpected safety issues have been identified in the adult population.

Hyperphosphataemia was not reported in any subject in the paediatric safety database at the time of the initial MAA. Due to the mechanism of action, hyperphosphataemia was not an unexpected finding but an anticipated event already reflected in SmPC sections 4.2 and 4.4. Furthermore, the MAH proposed to amend SmPC section 4.8 for the adult population with hyperphosphataemia, which is endorsed. However, hyperphosphataemia may reflect over suppression of FGF23. According to PK/PD simulation results, there is an increased risk of hyperphosphataemia following burosumab 0.8 mg/kg Q2W suggesting that this lower dose level, administered more frequently, would not be desirable to use in the adult population. Hence, the 1 mg/kg Q4W dosing is endorsed for the adult population.

20/134 (15%) of the subjects in UX023-CL303 had pre-existing Anti-drug antibodies (ADA). Of those, 7/20 subjects were ADA negative after baseline and none of the 13/20 continuously positive after baseline had an increase in antibody titre during treatment.
Eight subjects were reported with treatment emergent ADA. These subjects had transient immune responses, with ADA-positive samples at only 1 or 2 post-treatment time points. No neutralising activity was detected in any of the ADA-positive subjects. The MAH was asked to present the occurrence of TEAEs of injection site reactions (ISRs) and hypersensitivity for patients who were ADA positive and ADA negative for both adult and paediatric populations. The presented data did not indicate that immunogenicity has an impact on TEAEs of ISRs or hypersensitivity AEs.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 2.1 during the procedure.

The PRAC considered that the risk management plan version 2.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Hyperphosphataemia • Ectopic mineralisation • Female reproductive toxicity • Increased parathyroid hormone levels
Missing information	• Elderly patients ≥65 years • Patients with mild to moderate renal impairment • Long term use

Pharmacovigilance plan

Study	**Summary of objectives**	**Safety concerns addressed**	**Protocol link Milestones**
Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children and Adults with X linked Hypophosphataemia category 3	Primary objectives: 1) To evaluate the frequency and severity of safety outcomes in children aged >1 year with radiographic evidence of bone disease, adolescents with growing skeletons and radiographic evidence of bone disease, and adults, treated with burosumab, including but not limited to: death, hospitalisations, cardiovascular disease, cancer, hyperphosphataemia and its complications, ectopic mineralisation and increased parathyroid hormone levels; 2) To prospectively evaluate the frequency and outcomes of pregnancies in female patients treated with burosumab; 3) To prospectively evaluate the frequency and severity of safety outcomes in patients with mild to moderate chronic kidney disease at baseline treated with burosumab Secondary objectives: 1) To perform a retrospective cohort study using data from the registry to compare the safety outcomes of interest in patients exposed to burosumab to those in patients receiving alternative treatments for XLH	Long-term safety, hyperphosphataemia, ectopic mineralisation, increased parathyroid hormone levels, pregnancy effects and effects in patients with mild to moderate chronic kidney disease at baseline	Final study report submission: 2028 Start of data collection: Within 3 months of initial PASS approval. End of data collection: 2028 Study progress reports: Annually First interim report of study results: After 50 patients have achieved at least 6 months of duration in the PASS. Second interim report of study results: December 2023 Final study report: December 2028

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measure(s)
Hyperphosphataemia	See proposed text in SmPC (Annex 2) • Section 4.2 Posology and method of administration: Posology • Section 4.3 Contraindications • Section 4.4 Special warnings and precautions for use: Concurrent medication use, Hyperphosphataemia • Section 4.9 Overdose	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measure(s)
Ectopic mineralization	See proposed text in SmPC (Annex 2) • Section 4.2 Posology and method of administration: Posology • Section 4.4 Special warnings and precautions for use: Ectopic mineralization • Section 5.3 Preclinical safety data	None
Serious hypersensitivity	See proposed text in SmPC (Annex 2) • Section 4.3 Contraindications • Section 4.4 Special warnings and precautions for use: Hypersensitivity • Section 4.8 Undesirable effects: Skin reactions, Immunogenicity	None
Female reproductive toxicity	See proposed text in SmPC (Annex 2) • Section 4.6 Fertility, pregnancy and lactation: Pregnancy, Breast-feeding, Fertility • Section 5.3 Preclinical safety data	None
Increased parathyroid hormone levels	See proposed text in SmPC (Annex 2) • Section 4.4 Special warnings and precautions for use: Ectopic mineralization	None
Use in elderly (≥65)	None	None
Use in patients with severe renal impairment	See proposed text in SmPC (Annex 2) • Section 4.2 Posology and method of administration: Posology: Special Populations: Renal impairment • Section 4.3 Contraindications	None
Long term use	None	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC

guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

2.7.1. User consultation

No full user consultation with target patient groups on the Package Leaflet has been performed on the basis of a bridging report making reference to the original MAA for Crysvita. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

X-linked hypophosphataemia (XLH) is characterised by high levels of circulating fibroblast growth factor 23 (FGF23) that leads to excessive urinary phosphate excretion and subsequent hypophosphataemia, resulting in defective bone mineralisation and impacts to other tissues such as muscle.

The major pathologic consequences of XLH in bone are rickets, osteomalacia, fractures and bone deformities requiring surgical intervention. XLH in children is associated with substantial skeletal deformities that cause pain and impair physical functioning, such that a young child may be severely limited in his/her daily activities and will suffer lifelong disability, social stigmatisation, and pain as these deformities become a permanent structure of their bones. In adults, the chronic osteomalacia often leads to development of short stature, bowed limbs, pathologic fractures and pseudofractures, early osteoarthritis, and enthesopathies, which cause stiffness, and pain requiring use of analgesic drugs. These impairments may limit physical function and impact quality of life.

Burosumab is a recombinant fully human IgG1 monoclonal antibody that binds to and inhibits the excessive biological activity of FGF23, thereby treating the underlying cause of XLH.

3.1.2. Available therapies and unmet medical need

Conventional therapy for XLH consists of multiple daily doses of oral phosphate often combined with active vitamin D. In children, burosumab is approved in the EU for the treatment of XLH.

Despite the consensus regarding conventional treatment of children with XLH, its efficacy in improving skeletal outcomes has not been demonstrated in prospective, randomised clinical trials.

In adults, oral phosphate and active vitamin D therapy may be initiated (or maintained) for the treatment of osteomalacia, bone/joint pain and other symptoms, and pathologic fractures or pseudofractures (Carpenter et al, 2011; Linglart et al, 2014; Haffner et al, 2019), but evidence of efficacy to improve osteomalacia, bone mineral density, microarchitecture or pain in adults is limited or the data shows absence of positive effect (Sullivan et al, 1992; Shanboghue et al, 2018).

Furthermore, multiple daily doses of oral phosphate produce a transient and intermittent increase in serum phosphorus (Glorieux et al, 1980) that can exacerbate phosphate wasting because the impairment in renal phosphate reabsorption is not addressed. This intermittent phosphate load triggers high urinary phosphate excretion and increases risk and progression of nephrocalcinosis, also in adolescents who would have received shorter periods of oral therapy.

In the light of this, an unmet need for a specific treatment of XLH in adolescents and adults is acknowledged.

3.1.3. Main clinical studies

The primary evidence of burosumab efficacy in adults with XLH comes from Study UX023-CL303. Supportive efficacy data are provided from Study UX023-CL304, Study UX023-CL203 and the two phase 1/2 studies KRN23-INT-001 and KRN23-INT-002.

UX023-CL303 is an ongoing randomised, double-blind, placebo-controlled, Phase 3 study with open-label extension to assess the efficacy and safety of burosumab SC Q4W 1.0 mg/kg in XLH patients 18-65 years (N = 134; 68 burosumab, 66 placebo). The planned study duration is up to 157 weeks. The placebo-controlled double-blind phase was 24 Weeks. At this time point, Week 48 data is presented.

UX023-CL304 is an ongoing open-label, single-arm, Phase 3 study to evaluate the effects of burosumab SC Q4W 1.0 mg/kg on osteomalacia by bone biopsies in XLH patients 18-65 years (N = 14). The planned study duration is up to 144 weeks. At this time point, Week 48 data is presented.

KRN23-INT-001 was a 120-day long Phase 1/2, open-label, repeat-dose, dose-escalation study of KRN23 in XLH patients ≥18 years (N = 32; 28 burosumab, 1 placebo; 3 subjects discontinued before treatment) investigating the effect of burosumab SC Q4W 0.05, 0.1, 0.3 and 0.6 mg/kg.

KRN23-INT-002 was an open-label, long-term, 12-month extension study to KRN23-INT-001 (N = 23; 22 burosumab, 1 placebo) with dose-escalation (burosumab SC Q4W 0.1, 0.3, 0.6, and 1.0 mg/kg).

UX023-CL203 is an ongoing, Phase 2b, open-label, long-term extension study to KRN23-INT-001 and KRN23-INT-002 (N = 20). The planned study duration is 194 weeks. Data is currently available for all subjects to Week 48. Available doses are burosumab SC Q4W 0.3, 0.6, and 1.0 mg/kg.

3.2. Favourable effects

Serum phosphate

The primary endpoint of study UX023-CL303 was the proportion of subjects achieving mean serum phosphorus levels above the lower level of normal (LLN; 2.5 mg/dL [0.81 mmol/L]) at the midpoint of the dose interval (i.e., 2 weeks after each dose of study drug, the time of peak PD effect), as averaged across dose cycles between Baseline and Week 24.
The primary endpoint was met as 94.1% (95% CI 85.8, 97.7) of the subjects in the burosumab arm achieved mean serum phosphorus levels above LLN compared to 7.6% (95% CI 3.3, 16.5) in the placebo arm ($p<0.0001$).

The results from the selected secondary phosphate endpoints are summarised below.

- Proportion of subjects achieving a mean serum phosphorus concentration above the LLN across the ends (time of trough PD effect) of the dose intervals through Week 24: placebo 6% (95%CI 2.4, 14.6), burosumab 68% (95%CI 55.8, 77.6).
- Mean Change (SD) from Baseline at the midpoint of each dose cycle, as averaged across dose cycles (mg/dL): placebo 0.16 (0.272), burosumab 1.21 (0.510).
- Mean Change (SD) from Baseline at the end of each dose cycle, as averaged across dose cycles (mg/dL): placebo 0.13 (0.265), burosumab 0.69 (0.392).

Primary and secondary phosphate endpoints from the open-label studies support the results from study UX023-CL303.

Patient recorded outcomes (PRO)

Only PRO data from the placebo-controlled, double-blind period of UX023-CL303 are discussed below. The Brief Pain Inventory (BPI) scales are 10-point scales from 0 (no pain) to 10 (as bad as you can imagine). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scales ranges from 0 (best health state) to 100 (worst).

The BPI Worst Pain score at week 24 was the only originally prespecified key secondary endpoint. The mean worst pain decreased in the placebo group from 6.5 to 6.1 and from 6.8 to 5.8 in the burosumab group. The LS Mean [SE] Change from Baseline was -0.32 (0.22) in the placebo arm and -0.79 (0.21) in the burosumab arm (p=0.092).

During the study two additional key secondary endpoints were amended, WOMAC Physical Function score and WOMAC Stiffness score.

In the burosumab arm, WOMAC Physical Function score decreased from 51 to 43 points between baseline and Week 24 compared to from 44 to 43 in the placebo arm. The LS Mean [SE] Change from Baseline was +1.8 (2.7) in the placebo arm and -3.1 (2.6) in the burosumab arm (p=0.048).

In the burosumab arm, WOMAC Stiffness score decreased from 65 to 54 points between baseline and Week 24 compared to from 61 to 60 in the placebo arm. The LS Mean [SE] Change from Baseline was +0.5 (3.1) in the placebo arm and -7.8 (3.0) in the burosumab arm (p=0.011).

Applying the Hochberg adjustment for multiple testing for the three endpoints, the difference between the treatment arms in BPI Worst Pain and WOMAC Physical Function score was not significant at the $p<0.05$ and $p<0.025$ level, respectively, whereas WOMAC Stiffness score at Week 24 was significant at the $p<0.0167$ level.

Upon request, the MAH has provided information on what could be considered minimal clinical important difference (MCID) for the key secondary endpoints. According to the MAH, the MCID for adults with XLH are 1.72 for the BPI-SF Worst Pain score, 9.3 for the WOMAC Physical Function score, and 10.0 for the WOMAC Stiffness score. For WOMAC Stiffness, mean improvement corresponding to MCID was reached by approximately Week 36 and for WOMAC Physical function beyond Week 96, whereas the mean improvements did not reach MCID for BPI Worst pain during the course of the study.

The secondary endpoints in UX023-CL303 also included BPI Pain Severity, BPI Pain interference, Brief Fatigue Inventory (BFI; range 1-10) Worst Fatigue, and BFI Global Fatigue. There was a trend towards a favourable effect of burosumab in BPI Pain Severity score (LS mean difference between the treatment arms -0.4 [0.25]); however, no difference between the treatment arms was seen in BPI Pain interference, BFI Worst Fatigue, and BFI Global Fatigue. Also, no meaningful difference between the treatment arms in Patient's Global Impression of Improvement (PGI-I) was seen at Week 24.

Fracture/pseudofracture healing and enthesopathy

In study UX023-CL303, enthesopathy and healing of active fractures and pseudofractures detected by x-ray at baseline to the end of the study were exploratory endpoints.

At baseline, 14 active fractures and 51 active pseudofracture were reported in the burosumab arm. In the placebo arm, 13 active fractures and 78 active pseudofractures were reported.

The results at Week 24 are summarised below:

- Healed active fractures: burosumab 7/14 (50%), placebo 0/13 (0%)
- Partially healed active fractures: burosumab 3/14 (21%), placebo 6/13 (46%).
- Healed active pseudofractures: burosumab 21/51 (41%), placebo 7/78 (9%)

- Partially healed pseudofractures: burosumab 13/51 (26%), placebo 22/78 (28%)
- New findings from baseline to Week 24: burosumab 6, placebo 8

The results at Week 48 are summarised below:

- Healed active fractures: burosumab 8/14 (57%), placebo 6/13 (46%)
- Partially healed active fractures: burosumab 2/14 (14%), placebo 4/13 (31%).
- Healed active pseudofractures: burosumab 33/51 (65%), placebo 26/78 (33%)
- Partially healed pseudofractures: burosumab 9/51 (18%), placebo 32/78 (41%)
- New findings from Week 24 to Week 48: burosumab 1, placebo 3

No comparison in fracture healing between the treatment arms was planned. In a post-hoc analysis using a hierarchical generalised linear mixed proportional odds model showed an odds ratio between burosumab vs placebo for fracture healing of 16.8 (95% CI 4.9, 57.0; p<0.0001).

Adult patients with XLH often have calcification of tendons and ligaments (enthesopathy) at sites of insertion into bone. Total calcaneal enthesopathy burden was added as an exploratory endpoint in protocol amendment 1. Therefore, few subjects completed this assessment at both Baseline and at Week 24.

The results are shown below:

- Mean (SD) total calcaneal enthesopathy burden at Week 24: burosumab (N=12) 5.90 (3.56) cm, placebo (N=10) 4.07 (2.38) cm
- The LS mean (SE) change from Baseline to Week 24: burosumab -0.47 (0.64) cm, placebo -1.55 (0.70) cm (p=0.26)
- Mean (SD) total calcaneal enthesopathy burden at Week 48: 5.25 (3.03) cm (N=52), placebo→burosumab group 5.99 (3.07) cm (N=45)
- The LS mean (SE) change from Baseline to Week 48: burosumab→burosumab (N=52) -0.53 (0.21) cm, placebo→burosumab (N=45) -0.12 (0.224) cm

Bone mineralisation

The primary objective in study UX023-CL304 was to establish the effect of burosumab treatment on improvement in XLH-associated osteomalacia (defective bone mineralisation) as determined by ration between osteoid (unmineralized bone) volume and total bone volume (OV/BV) by iliac bone biopsies. OV/BV is elevated in osteomalacia.

The study met its primary endpoint as the OV/BV ratio decreased by 54% from baseline to Week 48 (p<0.0001). This was supported by a decrease in osteoid (unmineralized bone) surface area/total bone surface area (OS/BS) (-26%; p=0.0002) and osteoid thickness (O.Th) (-32%; p<0.0001).

At Baseline, all eleven subjects in Study UX023-CL304 had osteomalacia as determined by evaluation of the iliac crest bone biopsy. In the qualitative analysis of the bone biopsies at Week 48, although improved in 10/11 subjects, some grade of osteomalacia remained in all subjects.

This data is supported by burosumab effect on the bone formation marker P1NP and the bone resorption marker CTx. For both markers, a marked increase was seen on burosumab treatment, reaching maximum after 12-24 weeks of treatment. The serum concentrations of both markers however remain above baseline values at Week 96 in both Study UX023-CL303 and UX023-CL304. The increase in P1NP seemed

to be both more pronounced and sustained than that of CTx in both studies, suggesting a positive remodelling balance with a net increase in bone formation.

Six-minute walking test (6MWT)

6MWT was an exploratory endpoint in UX023-CL303.

At Baseline, the mean (SD) actual distance walked was 356.8 (109.46) m (range: 55 – 643 m) in the burosumab group and 367.4 (103.41) m (160 – 615 m) in the placebo group.

At Week 24, the LS mean (SE) change from Baseline was 14.8 (7.67) m in the burosumab group and -5.0 (7.54) m in the placebo group; the LS mean difference between treatment groups was 19.8 (7.67) m (p = 0.0108).

The LS mean (SE) change from Baseline to Week 48 was 30.5 (6.93) m in the burosumab→burosumab group and 20.2 (8.76) m in the placebo→burosumab group.

3.3. Uncertainties and limitations about favourable effects

Originally, one single key secondary endpoint, BPI Worst Pain score at week 24, was prespecified in the protocol for study UX023-CL303. During the course of the study, WOMAC Stiffness and Physical Function domains were elevated to key secondary endpoints at the end of the double-blind treatment period. The MAH explained their late action with a wish to await more data from another study (UX023-CL001) before finally deciding on key secondary endpoints. After taking these results into consideration, the MAH decided that BPI Worst pain was not sufficient to address the spectrum of XLH symptomatology. In particular, according to the concept elicitation patient interviews, stiffness was the most prevalent and impactful XLH symptom. Therefore, the MAH decided to include WOMAC Stiffness and WOMAC Physical function as two supplementary key secondary endpoints in the study.

The statistical methodology used for the analyses of change from baseline for the key PRO endpoints has been questioned. The MAH was requested to confirm that the assumption of normality of the underlying data had been confirmed in all cases, particularly in relation to the primary and key secondary endpoints. The tests suggest that the change scores were non-normal for all measures. As requested, the MAH also reanalysed the key secondary endpoints using a repeated measures ANCOVA. To confirm the appropriateness of the ANCOVA method on these key secondary endpoints, further analysis for the normality of residuals and homogeneity of variance was presented to confirm the appropriateness of the ANCOVA method on these key secondary endpoints. This is accepted.

During the Placebo-controlled Treatment Period, five subjects in the burosumab group and none in the placebo group had treatment unblinded per protocol due to hyperphosphataemia. The MAH has clarified that although the notation was "subject unblinded", only the investigator was unblinded. In addition, two cases of accidental unblinding were reported in study UX023-CL303, both in the burosumab group. According to the MAH, again, only site personnel were unblinded. However, the wording describing the events could be interpreted as that one of the subjects was actually unblinded. Notwithstanding, this is not considered to have any impact on the outcome of the study.

Due to the erroneous stratification by baseline pain, there was an imbalance in pain intensity between the treatment arms, as BPI worst pain was >6.0 in 75% of the subjects in the burosumab versus 59% in the placebo arm. This may have impact in the Patient reported outcomes (PROs). Moreover, in a limited study population, double stratifications inevitably lead to some imbalances between the treatment arms for other baseline parameters, e.g. osteoarthritis and nephrocalcinosis were reported more often at baseline in the burosumab arm (69% vs 58% respectively for osteoarthritis and 16% vs 8% for nephrocalcinosis). Furthermore, use of opioids was more common in the burosumab arm, 25% vs 20% in the placebo arm.

Taken together, this may implicate that the treatment arms were not fully balanced regarding baseline pain and XLH manifestations. The MAH was asked to comment on the potential impact of this imbalance on the outcome of the study. Upon request, the MAH has conducted interaction analyses demonstrating that no significant interaction was identified for the primary endpoint. For the key secondary endpoints, one statistically significant interaction was detected, between presence of nephrocalcinosis at baseline and BPI Worst Pain (p= 0.0475). The observed interaction is difficult to interpret as nephrocalcinosis is normally asymptomatic.
The Applicant has provided Forest plots displaying subgroup analysis for five baseline parameters not fully balanced, i.e. use of pain medication, use of opioid pain medication, baseline presence of osteoarthritis and baseline presence of nephrocalcinosis, with regard to the three key secondary endpoints as requested. None of the subgroups showed a consistent additional benefit in favour of burosumab across these key secondary endpoints, above that seen in the All Subjects group. Although statistical significance was not shown for most subgroups, the point estimate favours burosumab in all subgroups for the three key secondary endpoints.

3.4. Unfavourable effects

The adult safety database comprises of 176 subjects having received at least one dose of burosumab in studies KRN23-INT-001/KRN23-INT-002, UX023-CL203, UX023-CL303 and UX023-CL304. The total cumulative exposure is 205 patient-years and the mean duration of exposure was 61 weeks.

96-100% of the subjects in the five studies were reported with a treatment emergent adverse event (TEAE), of which 55-64% were deemed as related to burosumab.
In total, one SAE assessed as possibly related to study treatment (one event of angioedema in UX023-CL203). In this case, a woman under treatment with both lisinopril and burosumab developed a life-threatening event of angioedema, assessed as possibly related to both drugs by the Investigator. The MAH, on the other hand, considers that, as the subject continued on study medication without rechallenge hypersensitivity reactions after discontinuation of lisinopril, a causal association to lisinopril is more likely.

The rates of reported TEAEs were comparable in both treatment arms during the placebo-controlled period of UX023-CL303 (94% in the burosumab arm and 92% in the placebo arm), whereas somewhat more TEAEs were deemed as treatment related in the burosumab arm (44% vs 39%). Two subjects (3%) in each treatment arm were reported with an SAE. No SAE was deemed as related to the study drug in UX023-CL303.
Most TEAEs were balanced between the treatment arms. TEAEs more common in the burosumab included back pain (14% vs 6% for burosumab and placebo, respectively), tooth abscess (13% vs 8%), restless legs (RLS; 12% vs 8%) vitamin D decreased (12% vs 5%), dizziness (10% vs 6%), constipation (9% vs 0%), and investigation (21% vs 14%). This is largely in line with the known safety profile of Crysvita.

No fatality was reported before data cut-off in the safety data base. The fatal event reported after the data cut-off in UX023-CL303 was clearly unrelated to the study drug.

Adverse events of special interest (AESI) for Crysvita is Injection site reactions (IRS), Hypersensitivity, Hyperphosphataemia, Ectopic mineralisation, Restless legs (RLS) and Anti-burosumab antibodies (ADA).

The incidence of ISR was the same in both treatment arms during the placebo-controlled period of study UX023-CL303 (12% in each arm), as were hypersensitivity TEAEs (5.9% vs 6.1% for burosumab and placebo, respectively).

In total, nine hyperphosphataemia TEAEs in eight subjects were reported in the adult studies, all in the burosumab arm of UX023-CL303. However, totally 18/174 subjects (10%) in the adult safety database

were reported with serum phosphorus levels above the upper limit of normal (ULN) at least at one occasion. No event of serum phosphorus above ULN was reported during placebo treatment. In eleven of these eighteen subjects, the dose was reduced.

In the limited safety database, there are no indications of an accelerated ectopic renal or cardiac mineralisation by burosumab.

20/134 (15%) of the subjects in UX023-CL303 had pre-existing ADA. Three of those had previously been treated with burosumab in another study. 7/20 subjects were ADA negative after baseline and none of the 13/20 continuously positive after baseline had an increase in antibody titre during treatment. Eight subjects were reported with treatment emergent ADA. These subjects had transient immune responses, with ADA-positive samples at only 1 or 2 post-treatment time points. No neutralising activity was detected in any of the ADA-positive subjects. The safety profile does not seem to differ between ADA-positive and ADA-negative subjects.

The MAH was asked to summarise safety data from subjects with baseline liver affection of any kind. In the adult repeat dose XLH studies, 55 out of a total of 176 subjects (31.3%) were found to have either a history of hepatobiliary disorder of any kind (n=16) and/or impairment in liver function tests (any value above upper limit of the normal range) (n=44) at baseline ("liver cohort"). Due to a low number of events, direct comparisons to the total study population is difficult, but there were no new safety concerns identified in the 55 subjects in the liver cohort. Of note, 8 of the 55 subjects (14%) in the liver cohort had TEAEs of abnormal liver function or hepatobiliary disorders, whilst 2 of 122 (2%) without liver impairment at baseline had TEAEs of abnormal liver function or hepatobiliary disorders.

3.5. Uncertainties and limitations about unfavourable effects

Whilst the overall safety profile in adults is generally in line with that seen in the paediatric population, long-term data in the adult population is still scarce. The MAH was asked to address this. Overall, in the data provided in their response, there were no new safety concerns or any relevant differences in safety profile with burosumab treatment beyond 6 or 12 months compared to the first 6 months. 65 subjects received burosumab for more than 2 years. The MAH has proposed to include adult patients in the ongoing PASS, which is endorsed. The two ongoing studies, DMP and SUNFLOWER, should also provide further safety information in this regard. The MAH's commitment to include other safety reports within PSURs is endorsed.

Due to the low number of subjects with treatment emergent antibodies, it is difficult to draw any firm conclusions from the impact analyses for efficacy and safety performed by the MAH. It is however reassuring that no neutralising ADA activity has been detected. Moreover, the MAH presented data indicating that there were no differences in occurrence of TEAEs of injection site reactions (ISRs) and hypersensitivity for patients who were ADA positive and ADA negative in both adult and paediatric populations. No new information on ADA after the data base lock for the MAA is available at this time point.

Hyperphosphataemia was not reported in any subject in the paediatric safety database at the time of the initial MAA. Due to the mechanism of action, hyperphosphataemia was not an unexpected finding but an anticipated event already reflected in SmPC sections 4.2 and 4.4. Furthermore, the MAH proposes to amend section 4.8 for the adult population to include hyperphosphataemia, which is endorsed.

14% of the subjects with baseline liver affection had TEAEs of abnormal liver function or hepatobiliary disorders, compared to 2% in the group without a history of hepatobiliary disorder of any kind and/or impairment in liver function tests. It is agreed with the Applicant that it is to be expected that any individual with underlying hepatic disorder or conditions predisposing to hepatic disease could be more

likely to experience hepatic related events, in the absence of health intervention intended to treat existing hepatic function abnormalities. The applicant should continue to monitor for hepatic related safety signals in burosumab treated patients as part of routine PV monitoring.

Simulations from the PK/PD model showed that burosumab exposure estimates are greater following burosumab 0.8 mg/kg Q2W dosing than burosumab 1.0 mg/kg Q4W and differences in PK translates to relatively smaller changes from baseline of serum phosphorus due to saturation of the PK/PD mechanism. For the clinical endpoint of serum phosphorus levels, the predicted levels at Cmin, Cavg, and Cmax are all similar between the regimens. It should be noted that at all exposure measures, the 95th percentile of serum phosphorus predictions are greater following 0.8 mg/kg Q2W than those for burosumab 1.0 mg/kg Q4W. Given that following burosumab 1.0 mg/kg Q4W administration to adults in Study UX023-CL303, events of hyperphosphataemia occurred, burosumab 0.8 mg/kg Q2W administration in adults may put this population at an increased risk for hyperphosphataemia.

3.6. Effects Table

Effects Table for Crysvita in the treatment of XLH in adults and adolescents with closed epiphyseal growth plates (data cut-off: June 08, 2017)

Effect	Short description	Unit	Treatment Burosumab	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Mean serum phosphorus >LLN at mid-intervals	Subjects achieving endpoint	n (%)	64 (94.1) 95% CI 85.8, 97.7	5 (7.6) 95% CI: 3.3, 16.5	P<0.0001	Placebo-controlled phase of UX023-CL303
Mean Serum phosphorus	Change from baseline at mid-intervals	mg/dL (SD)	1.21 (0.51)	0.16 (0.27)		Placebo-controlled phase of UX023-CL303
BPI Worst Pain score	LS Mean [SE] Change from Baseline	Scale points (1-10)	-0.79 (0.21)	-0.32 (0.22)	P=0.092	Placebo-controlled phase of UX023-CL303
WOMAC Physical Function score	LS Mean [SE] Change from Baseline	Scale points (1-100)	-3.1 (2.6)	+1.8 (2.7)	p=0.048	Placebo-controlled phase of UX023-CL303
WOMAC Stiffness score	LS Mean [SE] Change from Baseline	Scale points (1-100)	-7.8 (3.0)	+0.5 (3.1)	p=0.011	Placebo-controlled phase of UX023-CL303
Healed active fractures/pseudofractures	Proportion of findings at baseline	%	43	8		Placebo-controlled phase of UX023-CL303
New active fractures/pseudofractures	New findings from baseline to Week 24	n	6	8		Placebo-controlled phase of UX023-CL303

Effect	Short description	Unit	Treatment Burosumab	Control	Uncertainties / Strength of evidence	References
OV/BV	Mean (SD) reduction from baseline	% (SD)	-54.2 (20.2)	N/A	p>0.0001	Week 48 UX023-CL304
Unfavourable Effects						
All AE	Affected subjects	n (%)	64 (94.1)	61 (92.4)		Placebo-controlled phase of UX023-CL303
All SAE	Affected subjects	n (%)	2 (2.9)	2 (3.0)		Placebo-controlled phase of UX023-CL303
Hyperphosphataemia	Affected subjects	n (%)	4 (5.9)	0 (0)		Placebo-controlled phase of UX023-CL303
Hyperphosphataemia	Affected subjects	n (%)	18 (10.2)	0 (0)		Adult safety database
Restless legs	Subjects with TEAE	n (%)	8 (11.2)	4 (6.1)		-"-

Abbreviations: LLN – lower limit of normal, OV/BV – ratio osteoid volume/total bone volume

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The manifestations of XLH differ in children with growing skeleton and older adolescents and adults. In children, XLH is associated with rickets, bone deformities and impaired growth, which, if untreated leads to short stature when the epiphyseal growth plates close.
In adults, it is no longer possible to affect skeletal growth. The symptomatology in adults is characterised by premature osteoarthritis, enthesopathy (calcification of tendons, ligaments, and joint capsules), an increased risk of fracture/pseudofractures with impaired healing and an increased risk of osteoporosis, all due to a combination of osteomalacia (poor mineralisation of the bone) and residual damage from rickets in childhood. This is associated with pain and stiffness. Spinal stenosis and tooth abscesses/tooth infections in the absence of caries are also part of the clinical picture in adults. Furthermore, hypophosphataemia per se is believed to contribute with diffuse symptoms such as weakness, fatigue and bone and muscle pain. Whereas some of the adult XLH manifestations are considered modifiable, e.g. osteomalacia, others are not, e.g. enthesopathy and osteoarthritis.

Due to these differences, the indication for treatment partly differs between the two populations. The primary goal with treatment in children is to prevent slow growth and deformities of the long bones, i.e. bowing. Such treatment effects could be evaluated by standardised methods. In adults, on the other hand, the treatment is at least partly symptomatic. Therefore, the treatment effect of burosumab may be more difficult to assess in the adult population than in the paediatric population.

The choice of comparator (i.e., placebo) is acceptable due to the practical feasibility to perform a blinded study between standard of care (conventional XLH treatment with oral phosphate and active vitamin-D

analogues) given perorally several times daily and burosumab administered subcutaneously every fourth week. Nevertheless, this implies that it is not possible in the adult study program to draw any conclusions on burosumab efficacy compared to conventional phosphate/D-vitamin treatment.

The increase in serum phosphorus concentration with burosumab treatment in adults is considered solid and convincing. This is a clear indication that the effect of burosumab on FGF23 function in adults is consistent with the effect in the paediatric population. Even though serum phosphate could be seen as a surrogate pharmacodynamic marker for clinical effect, chronic hypophosphataemia is a major contributor to the pathophysiology of the disease as described above. It is anticipated that normalisation of serum phosphate may have a beneficial effect on modifiable XLH manifestations, e.g. improved bone calcification, and possibly also by decreasing the deterioration rate of irreversible XLH damages. In addition, normalisation of serum phosphate should have a direct positive effect on symptoms from low serum phosphate per se, e.g. muscle weakness and fatigue. The increase in serum phosphorus concentration shown with burosumab treatment in adults is therefore considered clinically relevant.

The key secondary endpoints are afflicted with some weaknesses. The treatment arms were not fully balanced regarding XLH manifestations at baseline, indicating that the disease burden may have been larger in the burosumab arm. To address any impact of this on the primary and key secondary endpoints, the MAH provided interaction analyses and subgroup analyses for the baseline parameters presence of osteoarthritis, presence of nephrocalcinosis, BPI Worst pain, use of pain medication, and use of opioids. As expected, no significant interaction was identified for the primary endpoint serum phosphate and any of the five baseline parameters. For the key secondary endpoints, one interaction was identified. However, the value of interaction testing is limited in such a small population as the power for detection of interactions is low and the results are difficult to interpret. The Applicant has provided Forest plots displaying post-hoc subgroup analysis for the above-mentioned five baseline parameters with regard to the three key secondary endpoints as requested. Although statistical significance was not shown for most subgroups, the point estimate favours burosumab in all subgroups for the three key secondary endpoints.

The burosumab effect on the original key secondary endpoint BPI Worst Pain was numerically modest and not statistically significant. The additional key secondary endpoints WOMAC physical function and WOMAC Stiffness both had a nominal p-value >0.005, but due to gatekeeping as well as the use of the Hochberg method for the three key secondary endpoints, only in WOMAC Stiffness scale, the difference between the treatment arms turned out statistically significant. Moreover, the baseline scores for WOMAC Physical function scale were not balanced between the treatment arms; in fact, the difference between the baseline score was similar to the difference between baseline and Week 24 score in the burosumab arm. Taking also the other secondary PRO endpoints into consideration, the results are not fully concordant. On the other hand, the MAH has provided relevant justification for the modest effect reported on the PRO scales. Bone biopsies in Study UX023-CL304 indicate that improvement of osteomalacia may continue beyond Week 48. Taken these data into consideration, the 24-week-long placebo-controlled period of the study may not have been sufficient to fully characterize the improvements in pain and physical function that result from improvements in the underlying bone disease. The MAH further argues that a similar effect as in the burosumab arm Week 0-24 was seen in the placebo → burosumab arm after transition to active treatment. This is acknowledged; however, keeping in mind the inherent difficulties in assessing self-reported data in an open-label setting.
Taken together, while the quantitative effect of burosumab on PROs is considered modest, the totality of these data and the consistency of effect among the assessments support the view that the effects are meaningful. It should however be noted that some of the XLH manifestations are considered irreversible while others are deemed modifiable with treatment. This may result in a heterogenicity in the population with a very different response to burosumab on XLH symptomatology.

The positive effect on 6MWT and fracture/pseudofracture healing are considered clinically relevant; however, up to Week 24, there was no meaningful difference in the rate of new fractures between the

treatment arms. As discussed above, this may reflect the slow restoration of bone structure. This is supported by a decreasing rate of new fractures with time. A beneficial effect of burosumab on bone structure is also supported by the bone formation and bone resorption markers P1NP and CTx being elevated above baseline beyond Week 96, indicative of an active bone remodelling and by the primary analysis from the bone biopsy study UX023-CL304 showing a decrease in osteoid volume.

The safety profile presented in this application is largely compatible with the known safety profile from the approved paediatric population. However, as opposed to the paediatric population where no events of hyperphosphataemia were reported in the clinical paediatric studies constituting the MAA for this population, Hyperphosphataemia was reported in approximately 10% of the adult subjects. Due to the mechanism of action, hyperphosphataemia was not an unexpected finding but an anticipated event. Hyperphosphataemia may reflect over-suppression of FGF23. According to PK/PD simulation results, there is an increased risk of hyperphosphataemia following burosumab 0.8 mg/kg Q2W suggesting that this lower dose level, administered more frequently, would not be desirable to use in the adult population. Hence, the 1 mg/kg Q4W dosing is endorsed for the adult population.

3.7.2. Balance of benefits and risks

A solid and convincing effect was seen with respect to serum phosphorus levels in the pivotal study. Even though serum phosphate could be seen as a surrogate pharmacodynamic marker for clinical effect, chronic hypophosphataemia is a major contributor to the pathophysiology and progression of the disease. The effect on subjective XLH manifestations as assessed by patient reported outcome scales was modest, but indicative of the effects being meaningful. However, in this context it should be noted that the effects may depend on the degree of irreversible damage. Further support for a positive treatment effect of burosumab is given by data on fracture healing and bone calcification. Therefore, based on the totality of data a positive effect of burosumab also in the adult population is considered established. The risk profile is considered to be in line with that of the approved paediatric population, apart from a potentially higher risk of hyperphosphatemia.

3.7.3. Additional considerations on the benefit-risk balance

Adolescents with closed epiphyseal growth plates have not been included in any clinical studies, neither in the paediatric nor the adult development program. The proposed posology for this population is based on PK/PD modelling and simulation. The simulated doses indicate that a dosing regimen of 0.8 mg/kg Q2W provide a meaningful dose, i.e. phosphorus levels within the normal range, for adolescent patients.

As the manifestations of XLH differs from subjects with open to subjects with closed epiphyseal growth plates, efficacy data cannot be extrapolated from younger children. However, there are no reasons to suspect that the burosumab effect would differ in any meaningful way between adults and adolescents with closed growth plates, provided a similar exposure.

In paediatric Study UX023-CL201, there were 11 adolescent subjects identified whose growth plates closed during the course of the study. For one of the eleven subjects, the last reading with open growth plates was the Week 64 reading. The remaining ten subjects had open growth plates at the Week 88 reading. No information on safety in adolescents with closed epiphyseal growth plates is considered to be available from this limited group.
Thus, the safety profile in adolescents with closed epiphyseal growth plates needs to be extrapolated from the paediatric and adult subpopulations. The safety profile in the paediatric and adult population are similar with a few exceptions, e.g. hyperphosphataemia and restless legs. There are no reasons to suspect that the safety profile with burosumab treatment would differ in any meaningful way in this specific population compared to younger children or adults, given that the exposure is comparable.

Thus, the B/R for burosumab in adolescents with closed epiphyseal growth plates is considered positive.

3.8. Conclusions

The overall B/R of Crysvita is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include treatment of adults with X-linked hypophosphataemia (XLH), and modification of the currently approved indication in children and adolescents, by removing the qualification 'with growing skeletons', in order to include treatment in children and adolescents with closed epiphyseal growth plates.
The application provides new week-48 data from Study UX023-CL304; a randomized, double-blind, placebo-controlled, phase 3 study with open-label extension to assess the efficacy and safety of KRN23 in adults with XLH.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated and the Package Leaflet has been updated in accordance. Furthermore, the annexes are brought in line with the latest QRD template version 10.1.
The updated RMP version 2.1 was agreed during the procedure.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.