23 June 2022
EMA/634749/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

CRYSVITA

International non-proprietary name: burosumab

Procedure No. EMEA/H/C/004275/II/0023

Note

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

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List of abbreviations

Abbreviation	Definition
1,25(OH)2D	1,25-dihydroxyvitaminD
6MWT	6-Minute Walk Test
AE	Adverse event
ADA	Anti-drug antibody
ADHR	Autosomal dominant hypophosphataemic rickets
ADR	Adverse drug reaction
ALP	Alkaline phosphatase
BALP	Bone-specific alkaline phosphatase
BFI	Brief Fatigue Inventory
BPI	Brief Pain Inventory
Cavg	Average concentration
CDC	Centre for Disease Control and Prevention
CI	Confidence interval
CL/F	Apparent clearance
Cmax	Maximum concentration
Cmin	Minimum concentration
CSR	Clinical Study Report
CTX	Carboxy terminal cross-linked telopeptide of type 1 collagen
CV	Coefficient of variation
E0	Baseline serum phosphorus
EC50	Half-maximal effect
ECHO	Echocardiogram
Emax	Maximum effect
ENS	Epidermal nevus syndrome
EU	European Union
FGF23	Fibroblast growth factor 23
HHD	Hand-held dynamometry
HRQoL	Health-related quality of life
ISS	Injection site reaction
ISR	Integrated summary of safety
KRN23	Burosumab

LLN	Lower limit of the normal range
LS	Least squares
mAb	Monoclonal antibody
MAH	Marketing Authorisation Holder
MCS	Mental Component Summary
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-propeptide
PCS	Physical Component Summary
PD	Pharmacodynamic
PHEX	Phosphate-regulating gene with homology to endopeptidases located on the X chromosome
PK	Pharmacokinetic
PMT	Phosphaturic mesenchymal tumours
PT	Preferred term
PTH	Parathyroid hormone
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
RSI	Request for Supplementary Information in Annex I of this report
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SE	Standard error
SF-36v2	36-Item Short Form Health Survey, version 2
SmPC	Summary of Product Characteristics
STS	Sit-to-Stand
$t_{1/2}$	Half life
TEAE	Treatment-emergent adverse events
TIO	Tumour-induced osteomalacia
TmP/GFR	Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate
TRP	Tubular reabsorption of phosphate

WAL	Weighted arm lift test
XLH	X-linked hypophosphataemia
V/F	Apparent volume of distribution
Yo	years old
Q2W, Q4W	Every second/fourth week

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Kyowa Kirin Holdings B.V. submitted to the European Medicines Agency on 17 December 2020 an application for a variation.

The following variation was requested:

Variation 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 and IIIB

Extension of indication to include treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged 1 year and over, based on data from two ongoing open-label clinical studies, UX023T-CL201 and KRN23-002, in adults with TIO (144-week data and 88-week data are available, respectively). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly. An updated RMP version 4.0 has also been submitted. The MAH also applied for one additional year of market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Crysvita was designated as an orphan medicinal product EU/3/18/2011 on 16 April 2018. Crysvita was designated as an orphan medicinal product in the following indication:

Treatment of phosphaturic mesenchymal tumour

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0254/2017 on the granting of a (product-specific) waiver.

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new 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	17 December 2020
Start of procedure	23 January 2021
CHMP Rapporteur Assessment Report	22 March 2021
CHMP Co-Rapporteur Assessment Report	19 March 2021
PRAC Rapporteur Assessment Report	25 March 2021
PRAC members comments	29 March 2021
Updated PRAC Rapporteur Assessment Report	1 April 2021
PRAC Outcome	9 April 2021
CHMP members comments	14 April 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 April 2021
Request for supplementary information (RSI)	22 April 2021
CHMP Rapporteur Assessment Report	22 November 2021
PRAC Rapporteur Assessment Report	22 November 2021
PRAC Outcome	2 December 2021
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	9 December 2021
Request for supplementary information (RSI)	16 December 2021
CHMP Rapporteur Assessment Report	24 May 2022
PRAC Rapporteur Assessment Report	30 May 2022
PRAC members comments	n/a
PRAC Outcome	10 June 2022
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	16 June 2022
Opinion	23 June 2022
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for CRYSVITA in comparison with existing therapies (Appendix 1)	23 June 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Tumour-induced osteomalacia (TIO) is a rare, serious, and debilitating condition caused by overproduction of fibroblast growth factor 23 (FGF23) by a tumour (Minisola et al. 2017). The causative tumours are typically phosphaturic mesenchymal tumours (PMTs), an extremely rare and heterogeneous set of bone and soft tissue tumours that have a distinct histological appearance (Folpe et al. 2004; Bahrami et al. 2009).

State the claimed the therapeutic indication

The therapeutic indication proposed by the Applicant is "*Crysvita is indicated for the treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised, in patients aged 1 year and over*."

Epidemiology

Phosphaturic mesenchymal tumours (PMT) can affect a wide age range of patients, but most cases occur in middle-aged adults. There does not seem to be a predisposition for the tumour to occur in either sex, but a small female predominance has been observed.

A recent European study has shown that the incidence of TIO in Denmark for the period 2008-2018 was estimated as being below 0.13 per 100,000 person years for the total population of the country and below 0.09 per 100,000 in adults. The prevalence of TIO was estimated to be no more than 0.70 per 100,000 persons for the total population and 0.26 per 100,000 persons in adults.

Aetiology and pathogenesis

Most PMTs are benign, although several cases of multifocal and malignant PMTs have been reported in the literature (Folpe et al. 2004; Weidner and Santa Cruz 1987; Yamada et al. 2017; Yavropoulou et al. 2018); however, PMTs aberrantly produce high levels of circulating FGF23.

FGF23 was initially identified as the protein encoded by the mutated gene in autosomal dominant hypophosphataemic rickets (ADHR), a hereditary disorder of phosphate wasting. Subsequently, FGF23 was found to be overexpressed in tumour tissue obtained from patients with TIO and was identified as the key causative factor of the phosphate wasting syndrome in these patients (Shimada et al. 2001). Although the underlying causes of ADHR, TIO, and X-linked hypophosphataemia (XLH) are unique, all conditions are characterised by elevated FGF-23, resulting in excessive renal phosphate wasting by impaired phosphate reabsorption, reduced vitamin D synthesis and chronic hypophosphataemia.

Clinical presentation, diagnosis

As PMTs are usually small and seldom give local symptoms, the symptomatology in TIO is normally related to skeletal consequences of poorly mineralised bone related to chronic hypophosphataemia, such as osteomalacia, fractures, and pseudofractures. These skeletal defects manifest as musculoskeletal pain, proximal muscle weakness, fatigue, and reduced health-related quality of life. In children, TIO is rarer than in adults, and the condition may present with generalised osteopenia, rickets, pseudofractures, bowing of the extremities, gait abnormalities, growth retardation, and pain in the bones, joints, and muscles (Jan de Beur 2005).

Since FGF23 levels observed in TIO are generally higher than those seen in XLH, the resultant hypophosphataemia and downstream clinical syndrome is often more severe. The greater severity of the downstream consequences and symptomatic manifestations of phosphate wasting may also result from the lack of adaptation, since TIO is an acquired condition. The average time from onset of symptoms to diagnosis of TIO is 2.5 years (Drezner 1999). The delay in diagnosis can be attributed to various factors, including the rarity of the condition, the nonspecific and broad nature of the presenting symptoms such as bone/muscle pain or fatigue, and serum phosphate not typically being assessed as part of routine blood chemistry.

Management

When possible, tumour resection is the first line of treatment for TIO and can be curative. However, identifying the location of the causative tumour is often difficult, despite functional and anatomical imaging. When tumour resection is feasible, FGF23 levels decrease within minutes of tumour removal (Colangelo et al. 2018), serum phosphate levels return to normal within days (Shane et al. 1997; Siris et al. 1987), and symptoms resolve within months (Yu et al. 2017; Kumar et al. 2015), depending on the severity of the disease, it may take up to a year for significant clinical improvement to be seen (Dadoniene et al. 2016).

Approximately 35% to 40% of patients with TIO have tumours that cannot be localised and therefore cannot be surgically excised (Chong et al. 2013; Imel et al. 2006). When the tumour cannot be located or when complete resection is not possible, medical treatment should be initiated (Minisola et al. 2017; Ruppe 2013).

Current medical management includes treatment with multiple daily doses of oral phosphate and active vitamin D analogues. The phosphate dose required to improve clinical symptoms is often limited by intolerable gastrointestinal side effects. In some cases, active vitamin D alone may be administered (Geller et al. 2007).
Oral phosphate/active vitamin D therapy improves symptoms in some patients with TIO (Zuo et al. 2017) but is ineffective in others (Breer et al. 2014; Wasserman et al. 2016). The regimen does not correct renal phosphate wasting, the underlying cause of hypophosphataemia, and resultant osteomalacia. In addition, oral phosphate therapy may exacerbate phosphate wasting by increasing the renal phosphate load since the impairment in renal phosphate reabsorption due to excess FGF23 is not addressed. The intermittent phosphate load also triggers high urinary phosphate excretion and increases the risk and progression of nephrocalcinosis and nephrolithiasis. In some instances, the compensatory increases in parathyroid hormone (PTH) may increase the risk of developing secondary or tertiary hyperparathyroidism, which in turn can lead to hypercalciuria, and thereby further increase the risk of nephrocalcinosis. As such, oral phosphate/active vitamin D treatment requires frequent monitoring to mitigate the risks of nephrocalcinosis, hypercalciuria, and hyperparathyroidism (Jan de Beur 2005).

Alternative treatment approaches, such as image-guided cryoablation, heat ablation using radiofrequency, and radiation therapy have shown varying degrees of success in TIO patients with inoperable tumours (Jadhav et al. 2014; Tarasova et al. 2013; Tella et al. 2017).

An unmet need for additional treatments of subjects with TIO with tumours that cannot be localised and therefore cannot be surgically excised is agreed with the MAH

2.1.2. About the product

Burosumab is a fully human recombinant human IgG1 mAb designed to bind to and thereby inhibit the biological activity of FGF23. Based on its mechanism of action of targeting excess FGF23, burosumab is only intended to address the FGF23-driven pathophysiology of TIO and is not expected to impact the natural course of the underlying tumour.

A conditional Marketing Authorisation for treatment of XLH in the paediatric population was granted in the EU on 19 Feb 2018.
Burosumab is currently approved in the European Union (EU) for the treatment of XLH in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.

Burosumab was approved in the United States on 17 Apr 2018 for the treatment of XLH in adult and paediatric patients 1 year of age and older; the indication was subsequently expanded on 27 Sep 2019 to include paediatric patients 6 months of age and older. A subsequent approval to extend the indication for treatment of TIO associated with PMTs was granted in the US in June 2020. Marketing Authorisation was also granted in Japan in September 2019 and South Korea in September 2020, for the treatment of patients with FGF23-related hypophosphataemic rickets and osteomalacia, which includes both XLH and TIO.

2.1.3. General comments on compliance with GCP

According to the MAH, Studies UX023T-CL201 and KRN23-002 were conducted in accordance with Good Clinical Practice (GCP).

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

A signed ERA justification statement is included. There are no major updates to this compared with that already registered within the dossier. The only changes reflect the proposed additional indication.

KRN23 is a human IgG monoclonal antibody and can reasonably be expected to be subject to the same degradative pathways and to have the same environmental impact as naturally occurring human antibodies, therefore due to their nature they are unlikely to result in a significant 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 Burosumab Clinical Development Programme in TIO

Study Identifier Study Design	Study Population	Study Objectives	Key Assessments	Test Product: Route, Regimen, Dosage, Duration	Status
UX023T-CL201 Open-label, Phase 2 (United States)	• Adults with TIO/ENS-associated osteomalacia[a] ≥ 18 years old • 17 subjects enrolled[b], including 14 subjects with TIO and 1 subject with ENS	• Effect of burosumab treatment on increasing serum phosphate levels in adults with TIO or ENS-associated osteomalacia • Effect of burosumab treatment on improvement in TIO/ENS-associated osteomalacia as determined by histomorphometric indices	• Serum phosphate • Other biochemical disease parameters: TmP/GFR, TRP, 1,25(OH)$_2$D • Bone biopsies to evaluate histomorphometric parameters (O.Th, OS/BS, OV/BV, Mlt) • Biochemical markers of bone turnover: BALP, CTx, P1NP, osteocalcin • Fracture and pseudofracture healing: ^{99m}Tc bone scans and radiography • Functional mobility and strength: 6MWT, STS test • Patient-reported outcomes: BPI, BFI, SF-36 v2 • Safety assessments	Burosumab: SC, Q4W [c], doses from 0.3 to 2.0 mg/kg Repeat dose up to 300 weeks	Ongoing - primary analysis complete. Efficacy and safety data available to Week 144 (UX023T-CL201 Week 144 CSR)
KRN23-002 Open-label, Phase 2 (Japan & Korea)	• Adults with TIO/ENS-associated osteomalacia[a] ≥ 18 years old • 13 subjects with TIO enrolled	• Evaluate the efficacy and safety of burosumab after 144-week Q4W SC administration to Japanese and Korean patients with TIO or ENS	• Serum phosphate • Other biochemical disease parameters: TmP/GFR, TRP, 1,25(OH)$_2$D • Biochemical markers of bone turnover: BALP, CTx, P1NP, osteocalcin • Fracture and pseudofracture healing: ^{99m}Tc bone scans and radiography • Functional mobility and strength: 6MWT, STS test • Patient-reported outcomes: BPI, BFI, SF-36 v2 • Safety assessments	Burosumab: SC, Q4W, doses from 0.3 to 2.0 mg/kg Repeat dose up to 144 weeks	Ongoing - primary analysis complete. Efficacy and safety data to Week 88 (KRN23-02 Week 88 CSR) Safety data available to Week 112

1,25(OH)2D = 1,25-dihydroxyvitamin D; 6MWT = 6-Minute Walk Test; BALP = bone-specific alkaline phosphatase; BFI = Brief Fatigue Inventory; BPI = Brief Pain Inventory; CSR = Clinical Study Report; CTx = carboxy terminal cross-linked telopeptide of type 1 collagen; ENS = epidermal nevus syndrome; FGF23 = fibroblast growth factor 23; 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-propeptide; *PHEX* = phosphate-regulating gene with homology to endopeptidases located on the X chromosome; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SC = subcutaneous; SF-36 v2 = 36-item Short Form Health Survey version 2; STS = Sit-to-Stand test; TIO = tumour-induced osteomalacia; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; TRP = tubular reabsorption of phosphate; XLH = X-linked hypophosphataemia.
a: Clinical diagnosis of TIO/ENS-associated osteomalacia based on evidence of excessive FGF23 that is not amenable to cure by surgical excision of the offending tumour/lesion (documented by investigator).
b: Includes two subjects who were found to be positive for *PHEX* mutations, indicating a diagnosis of XLH rather than TIO.
c: If trough levels of serum phosphate remain < 2.5 mg/dL after the dose is increased to 2.0 mg/kg Q4W, the dose frequency may be increased to Q2W. One subject received Q2W dosing from Week 136 to Week 144 (Protocol Amendment 5).

2.3.2. Pharmacokinetics

Burosumab PK and PD data were previously characterised and submitted for both adults and paediatric patients who have XLH. Sparse pharmacokinetic (PK) data of burosumab in the TIO patient population was collected in studies UX023T-CL201 and KRN23-002. To support the characterisation of burosumab PK and PK/PD, modelling and simulations were performed using data from the aforementioned adult TIO studies, and PK and PD data from adult and paediatric XLH patients, who were enrolled in the clinical trials KRN23-US-02, KRN23-INT-001, KRN23-INT-002, UX023-CL201, UX023-CL205, UX023-CL203, UX023-CL303, UX023-CL301, and UX023-CL304. Further, modelling and simulation using data from these studies were used to support dosing in paediatric patients who have TIO.

In summary, following single or repeat dose SC administrations, burosumab serum concentrations displayed an approximate mono-exponential decline. Apparent elimination half-life was estimated to approximately 19 days in the adult XLH patient population. 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

An updated electrochemiluminescence-based assay for the detection of anti-burosumab antibodies was used in Study KRN23-002; results showed the assay to be the same as the previously submitted method that was used for Study UX023T-CL201. Assays to measure burosumab concentrations in serum, and to evaluate immunogenicity (anti-drug antibodies [ADA]) and total and free (unbound) FGF23, serum phosphorus and bone turnover markers were described previously.

Validation Report P1833418

The method described in the validation report was used in study KRN23-002. This assay relies on the assay previously validated, which was part of EMEA/H/C/004275/II/0010/G.

A multitiered strategy (screening, confirmation, titer) was applied. Samples were first diluted with acid solution and incubated with excess of biotinylated KRN23 to capture the anti-KRN23 antibodies in a 96 well plate. Then the biotinylated KRN23 and anti-KRN23 antibodies complexes were captured with streptavidin magnetic beads. Subsequently, acid was added to dissociate the captured immunocomplexes and elute the antibodies. Biotinylated KRN23 and ruthenylated KRN23 in alkaline solutions were added to neutralize the acid and form immunocomplexes with anti-KRN23 antibodies. The immunocomplexes were added to a MSD streptavidin plate and then incubated. Finally, the plate was read to determine the electrochemiluminescence signals.

Table 2: Validation summary for the SPEAD-ECL ADA assay

Assay	Validation parameter	Result
Screening	Cut point (response ratio)	1.13
	Sensitivity	14.5 ng/mL of positive control
	Hook effect	Not observed
	Drug tolerance	100 µg/mL at 100 ng/mL of positive control 800 µg/mL at 500 ng/mL of positive control
	Selectivity (healthy, hemolysis and hyperlipidemia matrix)	Response ratio of LPC: 1.97 to 2.78 ECL response of LPC: 185 to 237 ECL response of blank: 81 to 135 ECL response of LPC treated with KRN23: 78 to 92
	Intra-assay precision	3.6% to 6.2%
	Inter-assay precision	5.6% to 11.0%
Confirmatory	Cut point (%Depletion)	26.93%
	Intra-assay precision	0.3% to 4.3%
	Inter-assay precision	0.4% to 8.1%
Titer	Titer reproducibility	81 (3/4 titers) and 27 (1/4 titers) at 2000 ng/mL of positive control

A full validation was performed (see Table 2). Anti-KRN23 monkey antibodies were used as the positive control (LPC 100 ng/mL, MPC 500 ng/mL and HPC 2000 ng/mL). 55 individual samples from healthy subjects analysed in 6 runs by 2 analysts were used for setting the respective cutpoints. In the screening assay, 13 outliers were removed using box plot analysis. As the response ratios were found normally distributed, the cutpoint was calculated at 5% false positive rate (FPR) using the parametric approach. In the confirmatory assay, 10 outliers were removed using the box plot analysis, and the cutpoint was calculated at 1% FPR using the parametric approach. Selectivity was demonstrated in individual samples (healthy, 10 individuals; haemolytic, 5 individuals; hyperlipidaemic, 5 individuals).

Population Pharmacokinetic Analysis

A population PK analysis was used to determine the characteristics of burosumab in subjects with TIO. Since the PK samples collected from the 27 subjects with TIO were sparsely sampled, a pooled analysis approach with data from adult and paediatric XLH patients was used to support the burosumab population PK model. PK and PD data from adult and paediatric XLH patients, who were enrolled in the clinical trials KRN23-US-02, KRN23-INT-001, KRN23-INT-002, UX023-CL201, UX023-CL205, UX023-CL203, UX023-CL303, UX023-CL301, and UX023-CL304, were included in the analysis. Study details for subjects with XLH were provided in the previous population PK and PK/PD report. Details on the dose regimens, planned PK and PK/PD schedules and number of subjects of the clinical trials for subjects with TIO are presented in Table 3.

Table 3: Summary of Burosumab Clinical Studies with Adult TIO Subjects Included in the Population PK and PK/PD Analyses

Study Number	Study Title	Planned Dose Regimens	Number of Subjects in the Analysis	PK/PD Sampling Included in the Analyses
UX023T-CL201	A phase 2 open-label trial to assess the efficacy of burosumab, an antibody to FGF23, in subjects with tumor-induced osteomalacia (TIO) or epidermal nevus syndrome (ENS)-associated osteomalacia	Starting dose of 0.3 mg/kg Q4W. Doses of burosumab will then be titrated in an effort to achieve a target fasting serum phosphorus range of 2.5 to 4.0 mg/dL. The maximum dose will be set at 2.0 mg/kg Q2W. Subjects will be treated with burosumab for up to 244 weeks.	16 subjects (i.e., 14 subjects with TIO and 2 patients with XLH) One subject with ENS was removed from the analysis	PK: Baseline, Day 1, Weeks 2, 4, 8, 16, 20, 22, 24, 32, 36, 40, 48, 120,148, 172, 196 PD: Predose at Screening, Baseline, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 21, 22, 24, 28, 32, 36, 40, 44, 48, 60, 72, 84, 96, 108, 120, 132, 142, 144, 148, 156, 160, 166, 168, 180, 190,192
KRN23-002	A phase 2 open-label trial to assess the efficacy and safety of burosumab in patients with tumor-induced osteomalacia or epidermal nevus syndrome	Starting dose at 0.3 mg/kg Q4W. The dose of burosumab was adjusted according to the dose adjustment criteria with maximum dose of 2.0 mg/kg, Q4W.	13 subjects (9 subjects enrolled in Japan and 4 subjects enrolled in Korea)	PK: Predose at Weeks 0, 1, 2, 4, 8, 16, 20, 21, 22, 24, 32, 36, 40 and 48 PD: Predose at Screening, Baseline, Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 24, 26, 28, 30, 32, 34, 36, 40, 42, 44, 46, 48, 56, 64, 72

ENS = Epidermal nevus syndrome; FGF23 = Fibroblast growth factor 23; PD= Pharmacodynamic; PK= Pharmacokinetic; Q2W= Biweekly (once every two weeks); Q4W= Monthly (once every four weeks); TIO = Tumor-induced osteomalacia

Data

A total of 306 subjects (27 with TIO and 279 XLH) treated with burosumab were included in the current population PK and PK/PD analyses. Among them, 94 were children (six subjects aged 1 to 2 years old and 88 subjects aged 2 to 12 years old) and 212 were adults. All the 27 subjects with TIO were adults. Descriptive statistics of baseline demographic data used in the current modelling are presented in Table 4 and Table 5.

Table 4: Summary of Continuous Demographic Data at Baseline in Subjects with TIO and XLH

Continuous Covariates	Mean (CV%) Median [Minimum-Maximum] Geom. Mean (Geom. CV%)		
	Adults with TIO (n=27)	Adults with XLH (n=185)	Paediatrics with XLH (n=94)
Age (years)[a]	58.6 (17.9%)	40.6 (30.2%)	6.90 (44.9%)
	58.0 [33.0, 73.0]	41.0 [18.5, 68.0]	7.50 [0.800, 12.8]
	57.6 (19.6%)	38.6 (33.3%)	5.97 (67.2%)
Height (cm)	160 (7.76%)	152[b] (7.01%)	109[c] (17.3%)
	160 [125, 187]	150 [121, 176]	110 [54.6, 146]
	159 (8.01%)	151 (7.10%)	107 (18.5%)
Baseline body weight (kg)	78.4 (30.3%)	71.7 (26.7%)	24.7 (44.3%)
	76.2 [36.4, 150]	69.0 [36.1, 140]	22.6 [9.00, 55.2]
	75.1 (31.0%)	69.2 (26.7%)	22.3 (48.2%)
BMI at baseline (kg/m^2)	30.3 (23.3%)	31.1[b] (26.7%)	20.0[c] (31.9%)
	30.0 [20.9, 51.6]	30.1 [17.4, 68.2]	18.3 [14.2, 67.8]
	29.6 (22.1%)	30.2 (25.2%)	19.4 (22.9%)

BMI = body mass index; CV = coefficient of variation; Geom = geometric; n = Number of patients; PHEX = phosphate-regulating gene with homologies to endopeptidases on the X chromosome; TIO = tumour-induced osteomalacia; XLH = X-linked hypophosphataemia.
a: Age at screening; b: n = 183; c: n = 92

Note 1: Height and BMI were missing for two patients in Study UX023-CL201 and one patient in Study UX023-CL303. Height of patient UX023-CL303-142-309 in Study UX023-CL303 was considered as outlier and was excluded from the summary statistics with BMI.
Note 2: Number of adult patients was based on the unique subject identifier (USUBJID); 26 patients with XLH were enrolled in more than one trial and for these patients, the first baseline values were considered.
Note 3: Two patients in Study UX023T-CL201 were tested as positive for PHEX mutation. Those two patients were included in the XLH population.

Table 5: Summary of Categorical Demographic Data at Baseline in Subjects with TIO and XLH

Categorical Covariates	**n (%)**		
	Adults with TIO (n=27)	**Adults with XLH (n=185)**	**Paediatrics with XLH (n=94)**
Sex			
Male	13 (48.1%)	118 (63.8%)	48 (51.1%)
Female	14 (51.9%)	67 (36.2%)	46 (48.9%)
Race			
White	12 (44.4%)	153 (82.7%)	83 (88.3%)
Black or African American	2 (7.4%)	5 (2.7%)	3 (3.2%)
Asian	13 (48.1%)	25 (13.5%)	2 (2.1%)
Other	0 (0%)	2 (1.1%)	6 (6.4%)
Anti-Burosumab Antibody[a]			
Negative	25 (92.6%)	152 (82.2%)	79 (84.0%)
Positive	2 (7.4%)	33 (17.8%)	15 (16.0%)

n = Number of patients; PK = pharmacokinetic; PHEX = phosphate-regulating gene with homologies to endopeptidases on the X chromosome; TIO = tumour-induced osteomalacia; XLH = X-linked hypophosphataemia.
a: At least one PK sample with presence of anti-burosumab antibody.
Note 1: Number of adult patients was based on the unique subject identifier (USUBJID); 26 patients with XLH were enrolled in more than one trial and for these patients, the first baseline values were considered.
Note 2: Two patients in Study UX023T-CL201 were tested as positive for PHEX mutation. Those two patients were included in the XLH population.

For the adult population, the median and distribution of baseline weight and BMI were similar between TIO and XLH populations. Sex appeared to be evenly distributed in TIO population included in the analyses. The majority of subjects with TIO were either Asian (48.1%) or White (44.4%).

Descriptive statistics of laboratory tests at the baseline are provided in Table 6.

Table 6: Summary of Laboratory Tests at Baseline in Subjects with TIO and XLH

	Mean (CV%) Median [Minimum-Maximum] Geom. Mean (Geom. CV%)		
	Adults with TIO (n=27)	**Adults with XLH (n=185)**	**Paediatrics with XLH (n=94)**
Bone alkaline phosphatase (µg/L)	39.6 (52.3%)	25.3 (69.7%)	120 (67.2%)
	34.0 [14.4, 98.6]	19.0 [3.00, 98.0]	122 [13.0, 396]
	35.2 (51.8%)	20.4 (73.8%)	88.2 (106%)
Serum albumin (g/dL)	4.28 (5.87%)	4.33 (6.85%)	4.47 (5.48%)
	4.20 [3.70, 4.80]	4.30 [3.40, 5.30]	4.50 [3.80, 5.30]
	4.27 (5.91%)	4.32 (6.89%)	4.46 (5.50%)
Serum alkaline phosphatase (U/L)	287 (65.5%)	122 (41.5%)	487 (26.5%)
	247 [98.0, 942]	113 [26.0, 338]	472 [237, 980]
	241 (64.4%)	113 (41.7%)	471 (26.7%)
Serum alanine aminotransferase (U/L)	29.6 (78.5%)	25.0 (66.3%)	16.0 (31.4%)
	21.0 [8.00, 105]	20.0 [7.00, 98.0]	15.0 [5.00, 31.0]
	23.7 (71.9%)	21.5 (56.1%)	15.2 (33.3%)
Estimated creatinine clearance (mL/min/1.73m2) in paediatric patients (mL/min) in adult patients	110[a] (32.0%)	146 (39.7%)	173[c] (27.5%)
	105 [62.6, 190]	131 [49.9, 387]	169 [100, 469]
	105 (32.7%)	136 (38.6%)	168 (24.2%)
Serum total intact FGF23 (PG/Ml)	696[a] (120%)	144[b] (182%)	324[d] (123%)
	356 [84.5, 2694]	77.1 [15.0, 2272]	172 [33.0, 2390]
	385 (150%)	87.2 (102%)	204 (111%)

BLQ = below limit of quantification; CV = coefficient of variation; FGF23 = fibroblast growth factor 23; Geom = geometric; LLOQ = lower limit of quantification; n = Number of patients; PHEX = phosphate-regulating gene with homologies to endopeptidases on the X chromosome; TIO = tumour-induced osteomalacia; XLH = X-linked hypophosphataemia.
a: n = 26; b: n = 168; c: n = 92; d: n = 93.
Note 1: Number of adult patients was based on the unique subject identifier (USUBJID); 26 patients were enrolled in more than one trial. The first baseline values were considered in those statistics.
Note 2: Two patients in Study UX023T-CL201 were tested as positive for PHEX mutation. In the descriptive statistics, those two patients were included in the XLH population.

Marked differences were observed in baseline levels of serum FGF23, bone and serum ALP between TIO and XLH populations. The median value of baseline FGF23 levels was 4.6-fold higher in adults with TIO than that in adults with XLH. The median baseline value of bone ALP was 1.8-fold higher in adults with TIO than that in adults with XLH. Similarly, median baseline serum ALP levels were 2.2-fold higher in adults with TIO than that in adults with XLH. Overall, these baseline data indicate that serum FGF23 levels were higher, and the bone manifestations associated with hypophosphataemia may be more severe in adult subjects with TIO, compared to adult subjects with XLH.

In both TIO studies all enrolled subjects began treatment with burosumab at a starting dose of 0.3 mg/kg (Week 0). In Study UX023T-CL201, following the titration period (Weeks 0-16), the median dose was 0.9 mg/kg at Week 20, 0.9 mg/kg at Week 48, 0.7 mg/kg at Week 96, and 0.6 mg/kg at Week 144. In Study KRN23-002, following the titration period (Weeks 0-16), the median dose was 0.7 mg/kg at Week 20, 0.8 mg/kg at Week 48, and 1.0 mg/kg at Week 88.

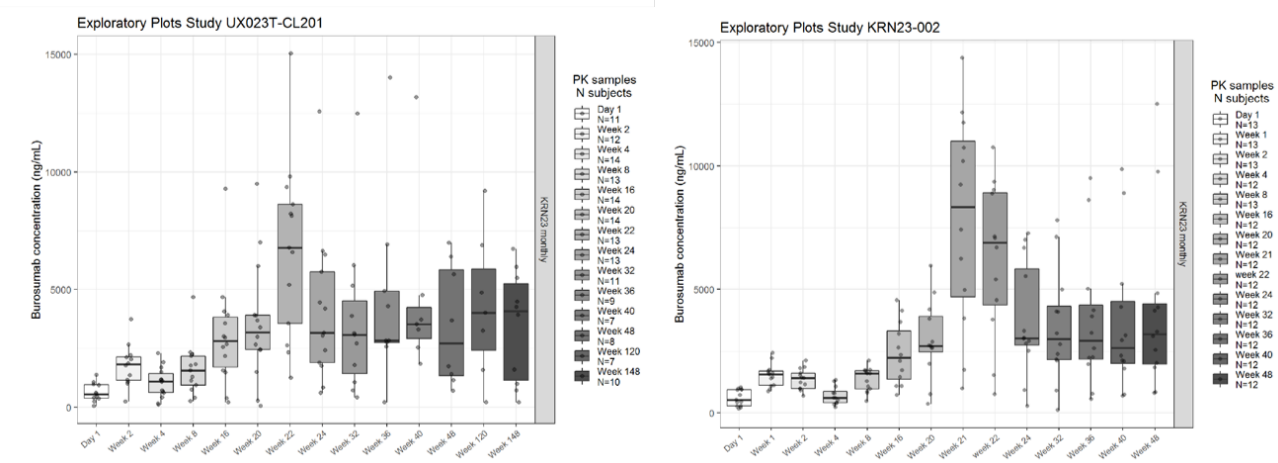
Numbers of individual samples of measurable and BLQ burosumab concentrations in TIO and XLH subjects are presented in Table and the distribution of observed burosumab concentrations in TIO subjects are visualised in Figure 1. In subjects with TIO, steady-state conditions were reached after approximately 20 weeks of the dosing titration period (i.e., similar trough medians), with median trough value of 3190 ng/mL in Study UX023T-CL201 and 2710 ng/mL in Study KRN23-002 (Figure 1) at Week 20. Median values at Week 22 (i.e., 2 weeks after the SC administration) were 6790 ng/mL and 6880 ng/mL for studies UX023T-CL201 and KRN23-002, respectively.

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

PK Samples	n (% within disease group)			
	Adults with TIO (n=363)	Adults with XLH (n=2848)	Pediatrics with XLH (n=1148)	Overall (n=4359)
AQL	0 (0.0 %)	2 (0.1%)	0 (0.0%)	2 (0.0 %)
BLQ	29 (8.0 %)	386 (13.6%)	52 (4.5%)	467 (10.7 %)
Exclude	0 (0.0 %)	1 (0.0%)	0 (0.0%)	1 (0.0 %)
Include	334 (92.0 %)	2459 (86.3%)	1096 (95.5%)	3889 (89.2 %)

ALQ = Above the limit of quantification (>9500 ng/mL); BLQ = Below the limit of quantification (Study specific: <36.0 or 50.0 ng/mL); n = Number of samples; PK = Pharmacokinetic; TIO = Tumor-induced osteomalacia; XLH = X-linked hypophosphatemia.
Note 1: 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.
Note 2: BLQ observed in blood samples from subjects enrolled in the placebo group were not included in the calculation
Note 3: In adult study UX023-CL203, two samples were ALQ of this specific study (i.e., >9500 ng/mL).

Figure 1: Distribution of Observed Concentrations of Burosumab in Subjects with TIO Stratified by Study



Model Development

Non-Linear Mixed Effect (NLME) population PK and PK/PD analyses were performed. Dataset exploration, figures and tables, as well as posterior Bayes estimation of exposure parameter values for individual subjects, as well as Monte-Carlo simulations, were performed using R® V3.5

The structural population PK model of burosumab previously developed for XLH subjects was re-evaluated with the updated dataset incorporating 334 additional PK samples collected from TIO studies (KRN23-002 and UX023T-CL201). Overall model evaluations suggest that the structural PK model developed for XLH was able to describe the PK of burosumab in subjects with TIO adequately, supporting a similar PK between the two disease populations. As a sensitivity analysis, the parameters were re-estimated with PK data collected only from TIO population and the results were compared to those obtained from the combined population. With the exception of CL/F, the relative differences between the PK parameters were less than 20%. The estimate of CL/F derived from TIO population was approximately 20% higher than that derived from the combined population, which was not considered clinically significant. As the integrated population PK model combing XLH and TIO populations provided more robust and stable parameter estimates, further model development for TIO proceeded with the combined PK datasets collected from both TIO and XLH populations.

The relationships between covariates and PK parameters were initially explored graphically to select potential covariates affecting the PK of burosumab. The following baseline covariates were explored: age, sex, body mass index (BMI), race, ethnicity, weight, height, serum FGF23, albumin, serum ALP, bone ALP, alanine aminotransferase, baseline creatinine, CrCL, country, study, and disease. No relevant trend was observed between PK parameters and respective covariates by graphical evaluations. To investigate covariates associated with TIO specifically, the effect of disease population (i.e., XLH vs. TIO) and serum

FGF23 at the baseline were further tested in the population PK model. Overall evaluations indicate that these two covariates did not influence burosumab PK to any extent that is statistically significant or clinically important. Therefore, the disease population and serum FGF23 at baseline were not retained in the final population PK model of burosumab.

Final Population PK Model

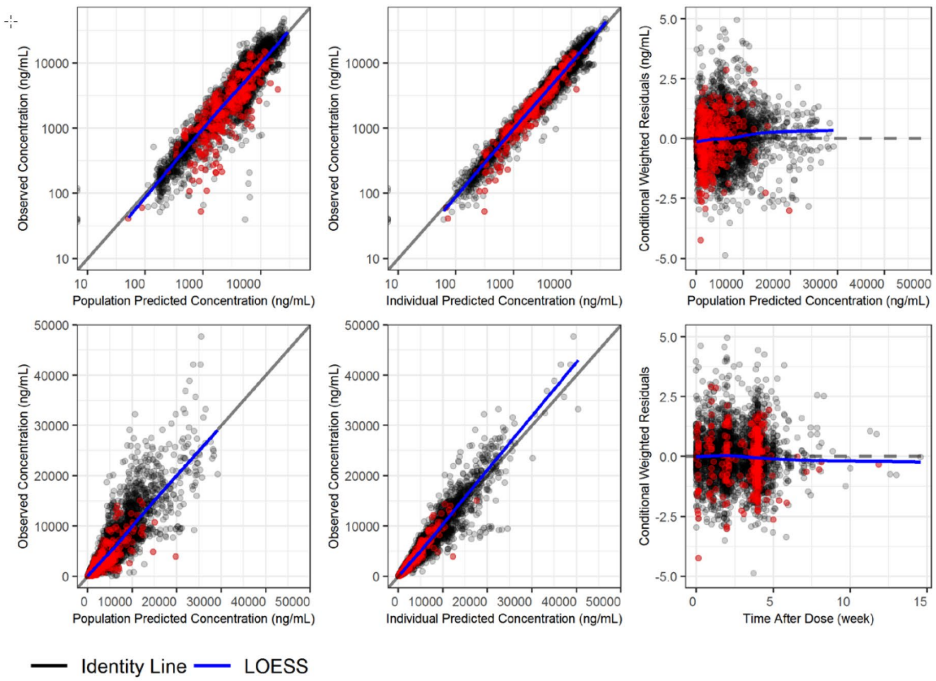
The final population PK model of burosumab was comprised of a first-order absorption from the SC injection, one-compartmental distribution, followed by the linear elimination. Body weight-based allometric scaling of CL/F and V/F was incorporated into the model. No other covariates were included in the final model. The population PK parameter values and associated uncertainties derived from the final model are presented in Table for a typical adult subject with TIO having a body weight of 70 kg. Model diagnostics as per Goodness-of-fit plots and visual predictive checks are displayed in Table 8 and Figure 2, respectively.

Table 8: Population PK Parameters of the Final Population PK Model for Burosumab in Subjects with TIO

PK Parameters	Typical Values (RSE%)	95th CI	BSV (%)	Shrinkage (%)
Ka (1/day)	0.379 (6.9)	0.328 – 0.431	0 FIX	
V/F (L)	7.45 (2.9)	7.02 – 7.87	33.5	17.1
WT effect on V/F	$\times (WT/70)^{0.914\ (3.7)}$	0.848 – 0.979		
CL/F (L/day)	0.284 (2.5)	0.271 – 0.298	34.8	3.9
WT effect on CL/F	$\times (WT/70)^{0.885\ (3.8)}$	0.819 – 0.952		
Additive error (ng/mL)	30.1 (20.2)	18.18 – 41.96		
Proportional error (%)	22.2			

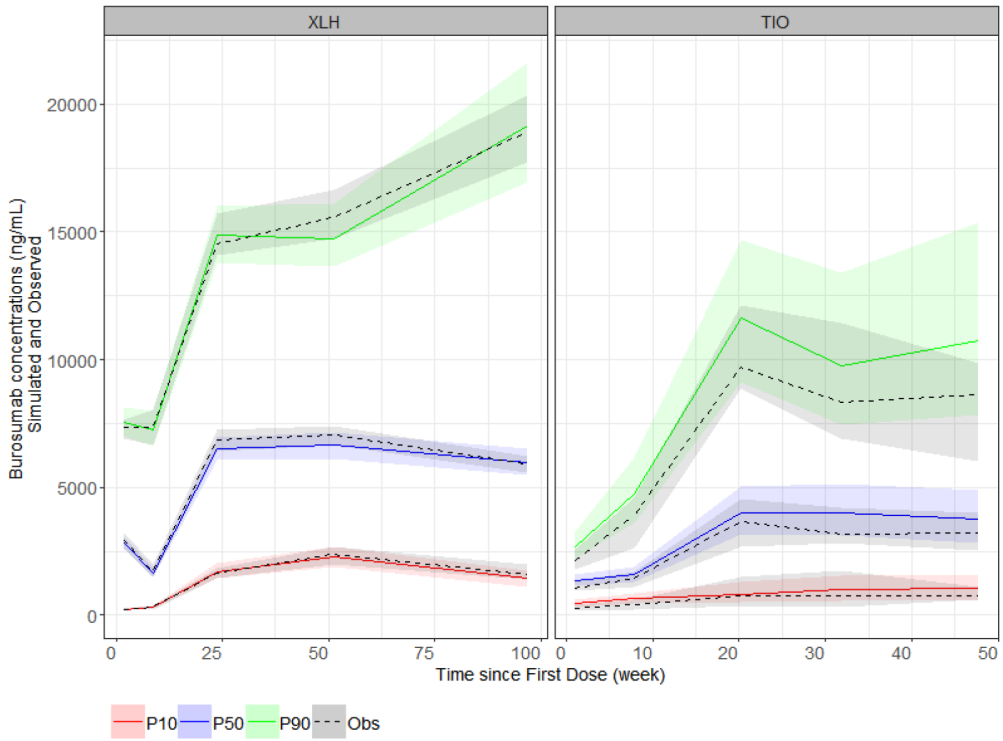
BSV = between-subject variability; CI = confidence interval; CL/F = apparent clearance; Ka = first-order rate of absorption; PK = pharmacokinetic; RSE = relative standard error; TIO = tumour-induced osteomalacia; V/F = apparent central volume of distribution; WT = body weight (kg); XLH = X-linked hypophosphataemia.
Note: Weight effect was centralised using 70 kg to facilitate the integration of adult data.
Source: ULTR-PMX-BUROSUMAB-1280/TIO, Table 8.

Figure 2: Goodness-of-Fit – Final Population PK Model of Burosumab in All Subjects



CWRES= Conditional weighted residuals; LOESS = Locally weighted scatter plot smoothing; TIO = Tumor-induced osteomalacia; XLH = X-linked hypophosphatemia.
Note 1: Red circles = Subjects with TIO; Black circles = Subjects with XLH.
Note 2: 7 samples had CWRES>4 and 2 samples had CWRES<-4.

Figure 3 Visual Predictive Check for Subcutaneous Administration of Burosumab in Subjects with TIO and XLH



Obs = Observations; P10 = 10th percentile; P50 = 50th percentile; P90 = 90th percentiles; PK = Pharmacokinetic; PI = Prediction interval; TIO = Tumor-induced osteomalacia; 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: PK data were regrouped into 10 bins with same number of samples by bin by population.
Note 3: Dashed lines represent percentiles of observed burosumab concentrations within each bin (90th percentiles in green, 50th percentiles in blue and 10th percentiles in red); shaded area represent 95% percentile interval of percentiles of predicted concentrations (90th percentiles in green, 50th percentiles in blue and 10th percentiles in red).

Based on the estimated absorption rate constant (Ka), the corresponding absorption half-life was approximately 43 hours (~1.8 days) suggesting that the absorption of burosumab would be completed within ~9 days (~5 × $t_{1/2}$), which should approximate the time to maximum concentration value of burosumab from SC administrations. The model-estimated CL/F and V/F suggest that burosumab is slowly cleared from the circulation with a limited distribution within body's extracellular water volume (~ 0.1 L/kg). These PK parameters for burosumab in subjects with TIO were similar to those previously obtained in subjects with XLH. In adult subjects with TIO having a median body weight of 76 kg, CL/F and V/F of burosumab were projected to be 0.305 L/day and 8.03 L, respectively. Corresponding elimination $t_{1/2}$ was projected to be ~18 days. Based on the predicted burosumab $t_{1/2}$ value, the time to reach ~90% PK steady state was approximately 64 days with a fixed dosing regimen.

Body weight was the only covariate included in the model to explain variability in CL/F and V/F as consistent with the previous analysis in subjects with XLH and is supportive of utilising a weight-adjusted administration regimen for burosumab. The model-based analysis indicates that baseline FGF23 did not affect the PK parameters of burosumab in subjects with TIO. As only two TIO subjects tested positive for ADAs over the entire treatment period a model-based analysis for ADA as a covariate was not possible in the current analysis. In the previous analysis with XLH studies, impact of ADA and NAb status on PK parameters of burosumab was deemed not significant.

Predicted exposure levels

The descriptive statistics of individual predicted (using the final burosumab PK model) burosumab exposure levels along with actual dose levels are presented in Table 9 with stratification by body weight.

Table 9: Descriptive Statistics of Individual Exposure Levels of Burosumab under Steady-State Conditions in Subjects with TIO Stratified by Body Weight Levels at Baseline

PK Parameters of Burosumab	Subjects with Baseline WT below median (≤76.2 kg) (n=14)	Subjects with Baseline WT above median (>76.2 kg) (n=13)	Overall (n=27)
Actual Burosumab Dose (mg)			
Mean (CV%)	60.2 (73.3%)	82.5 (70.0%)	70.9 (72.5%)
Median [Min, Max]	46.8 [3.90, 152]	88.0 [15.0, 180]	51.0 [3.90, 180]
Geom. Mean (Geom. CV%)	43.3 (124%)	61.7 (103%)	51.4 (114%)
WT-Adjusted Burosumab Dose (mg/kg)			
Mean (CV%)	0.942 (66.0%)	0.837 (68.3%)	0.891 (66.1%)
Median [Min, Max]	0.998 [0.103, 2.00]	0.896 [0.161, 2.08]	0.983 [0.103, 2.08]
Geom. Mean (Geom. CV%)	0.711 (107%)	0.645 (94.6%)	0.678 (98.4%)
Cmin of Burosumab (ng/mL)			
Mean (CV%)	3880 (76.7%)	4300 (81.3%)	4080 (77.9%)
Median [Min, Max]	3180 [582, 10000]	3580 [338, 12300]	3580 [338, 12300]
Geom. Mean (Geom. CV%)	2820 (112%)	2980 (129%)	2890 (116%)
Cmax of Burosumab (ng/mL)			
Mean (CV%)	8350 (65.4%)	9470 (71.6%)	8890 (67.9%)
Median [Min, Max]	7610 [1480, 18200]	7200 [2110, 22000]	7200 [1480, 22000]
Geom. Mean (Geom. CV%)	6590 (89.6%)	7270 (92.6%)	6910 (88.9%)
Cavg of Burosumab (ng/mL)			
Mean (CV%)	6260 (67.6%)	7040 (73.2%)	6640 (69.7%)
Median [Min, Max]	5730 [1180, 14500]	5740 [1170, 17700]	5740 [1170, 17700]
Geom. Mean (Geom. CV%)	4850 (94.2%)	5290 (100%)	5060 (94.8%)
AUC of Burosumab (µg × day/mL)			
Mean (CV%)	175 (67.6%)	197 (73.2%)	186 (69.7%)
Median [Min, Max]	161 [32.9, 407]	161 [32.8, 495]	161 [32.8, 495]
Geom. Mean (Geom. CV%)	136 (94.2%)	148 (100%)	142 (94.8%)

AUC= Area under the concentration-time curve over one dosing interval; Cavg= Average concentration; Cmax= Maximum concentration; Cmin= Minimum concentration; CV= Coefficient of variation; Geom = Geometric; Max = Maximum; Min = Minimum; n = Number of subjects; TIO = Tumor-induced osteomalacia; WT= Body weight
Note: Steady-state conditions were assumed for the simulations based on the last actual dose

2.3.3. Pharmacodynamics

Serum phosphate is the primary pharmacodynamic (PD) marker for burosumab and directly reflects its mechanism of action to inhibit FGF23 and restore renal phosphate reabsorption. This is further discussed under Clinical efficacy below.

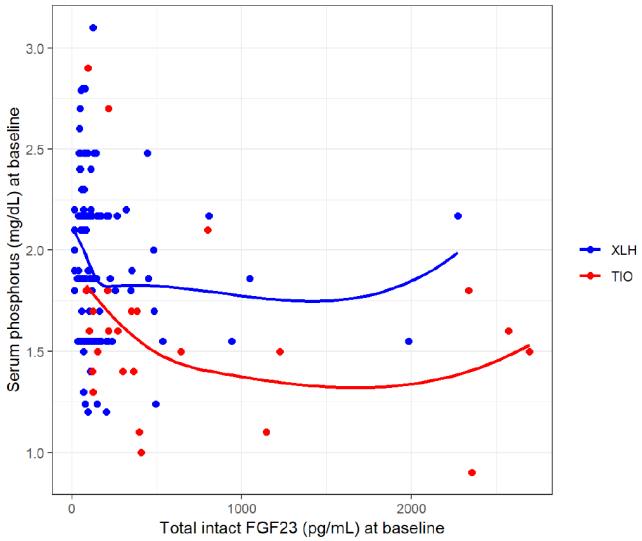
2.3.4. PK/PD modelling

The population PK/PD analysis was conducted based on the simulated burosumab PK profiles in individual subjects using the established population PK model, and time-matched, serum phosphate as the PD endpoint. The relationship between the serum levels of burosumab and phosphate have previously been explored in subjects with XLH (EMEA/H/C/004275/II/0000 and EMEA/H/C/004275/II/0010/G). A sigmoid Emax model described the observed serum phosphate following various regimens of burosumab via a SC route. A moderate but statistically significant effect of body weight on E0 and Emax were incorporated into the final model. The typical value of EC50 was 3819 ng/mL, which is time-invariant irrespective of subject's age and body weight (ULTR-PMX-BUROSUMAB-1280).

Data

A total of 298 patients (27 adults with TIO, 177 adults with XLH and 94 paediatrics with XLH) were included in PK/PD analysis. As illustrated in Figure 4, tentative negative relationships were observed between serum phosphorus and FGF23 levels at baseline in both populations (more pronounced in the TIO population) and the average levels of baseline serum phosphorus were lower in subjects with TIO. In adult subjects included in the PK/PD analysis, median of baseline FGF23 was about 4.8–fold higher in subjects with TIO, in comparison to the median observed in adults with XLH.

Figure 4: Relationship between Serum Phosphorus at Baseline and Total Intact FGF23 at Baseline in Adult Subjects with TIO and XLH



FGF23 = Fibroblast growth factor 23; LOESS = Locally weighted scatter plot smoothing; TIO = Tumor-induced osteomalacia; XLH = X-linked hypophosphatemia.
Note: Full lines represent the LOESS on observed data.

The number of individual data points of serum phosphorus levels stratified by the disease group available for the development of the population PK/PD model in subjects with TIO and XLH are presented in Table 10. Overall, a total of 8250 measurable concentrations of serum phosphorus were available for the development of the population PK/PD model in subjects with XLH and TIO, which is more than 2-fold the number of PK samples included in the population PK analysis (Table). The serum phosphorus concentrations collected in the TIO and XLH represented 8.7% and 91.3% of the overall PD dataset, respectively.

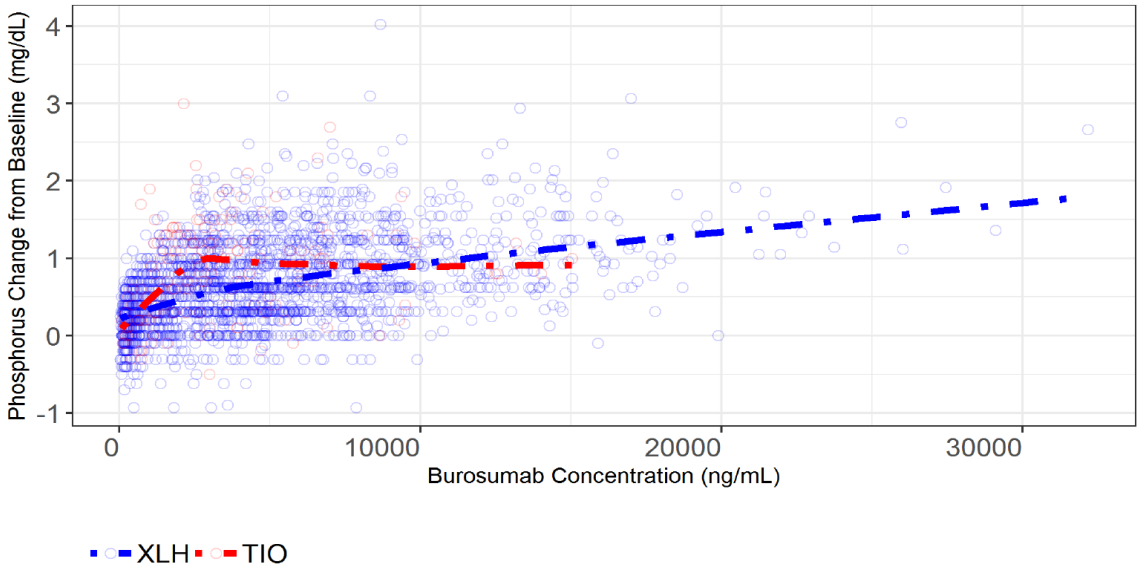
Table 10: Number of Serum Phosphorus Samples Available for the Population PK/PD Modelling

PD Samples	n (% of the overall)			
	Adults with TIO	Adults with XLH	Pediatrics with XLH	Overall
Included	719 (8.7 %)	5150 (62.4%)	2381 (28.9%)	8250 (100 %)

n= Number of samples; PD= Pharmacodynamic; TIO= Tumor-induced osteomalacia; XLH = X-linked hypophosphatemia.
Note: No PD data was available for Study KRN23-US-02

The relationship between individual predicted burosumab concentrations and serum phosphorus change from baseline observed in the 204 adult subjects included in the population PK/PD analysis is presented in Figure 5.

Figure 5: Relationship between Serum Phosphorus Change from Baseline and Individual Predicted Concentrations of Burosumab in Adult Subjects with TIO and XLH



LOESS= Locally weighted scatter plot smoothing; TIO = Tumor-induced osteomalacia; XLH = X-linked hypophosphatemia.
Note: The points are only for adult observations and dashed lines represent LOESS for each disease status.

Model development

An integrated PK/PD model was evaluated for its suitability to describe burosumab PK and PD data for the combined TIO and XLH datasets. A revised sigmoid Emax model was able to adequately describe the PK/PD relationship for the TIO and XLH populations. The effect of body weight on the model parameters was incorporated into the structural model.

The PK/PD relationship specific to subjects with TIO were explored further through the evaluation of relevant covariates on the model parameters. The relationships between covariates and PK/PD parameters were initially explored graphically to identify covariates affecting the PK/PD relationship between burosumab and serum phosphate. Graphical analyses indicated that no relevant trend was observed between model parameters and respective covariates except for FGF23 levels at the baseline. Since median baseline levels of serum FGF23 and ALP in subjects with TIO were markedly higher than those in subjects with XLH, these two covariates were formally tested in the population PK/PD model.

Final PK/PD Model for TIO Subjects

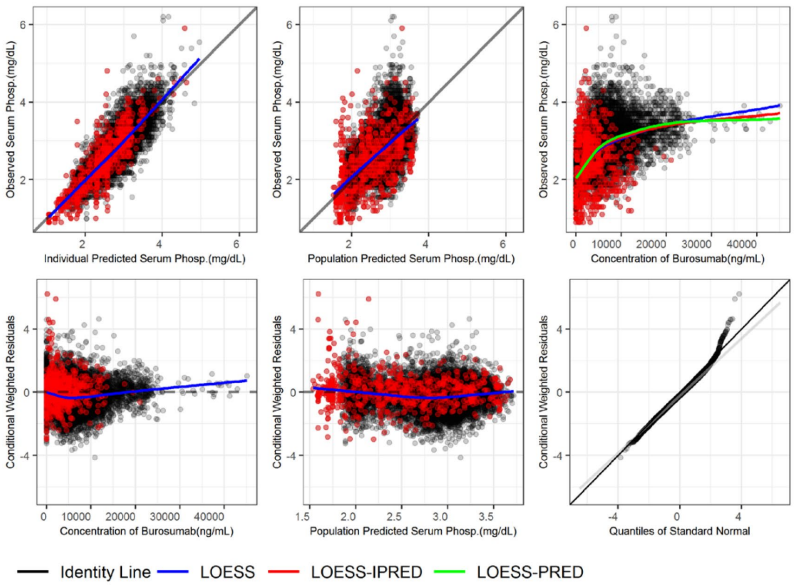
The final population PK/PD model in subjects with TIO was composed of a sigmoid Emax model including E0, Emax, EC50, and Hill coefficient. The time-varying body weight and the serum FGF23 at the baseline was retained as statistically significant covariates in the final model. The typical estimates of model parameters and associated uncertainties in subjects with TIO are presented in Table 6. Model diagnostics, presented as goodness-of-fit plots and visual predictive checks are visualised in XX and YY, respectively.

Table 11: Model Parameters of the Final Population PK/PD Model of Serum Phosphate in Subjects with TIO

PK/PD Parameters	Typical Values (RSE%)	95% CI	BSV (%)	Shrinkage (%)
E0 (mg/dL)	2.00 (1.3)	1.95 -2.05	13.6	10.3
Body weight effect on E0	$\times (WT/70)^{-0.144\ (-10.0)}$	-0.173 - -0.116		
FGF23 effect on E0	$\times (FGF23\ at\ baseline/356)^{-0.121\ (-48.5)}$	-0.236 - -0.006		
EC50 (ng/mL)	3538 (9.8)	2857 - 4219	99.9	23.7
FGF23 effect on EC50	$\times (FGF23\ at\ baseline/356)^{0.777\ (22.2)}$	0.44 - 1.11		
Hill coefficient	2.31 (20.5)	1.38- 3.23		
Emax (mg/dL)	1.31 (3.52)	1.18 - 1.44	45	22.5
Proportional error (%)	17.2			

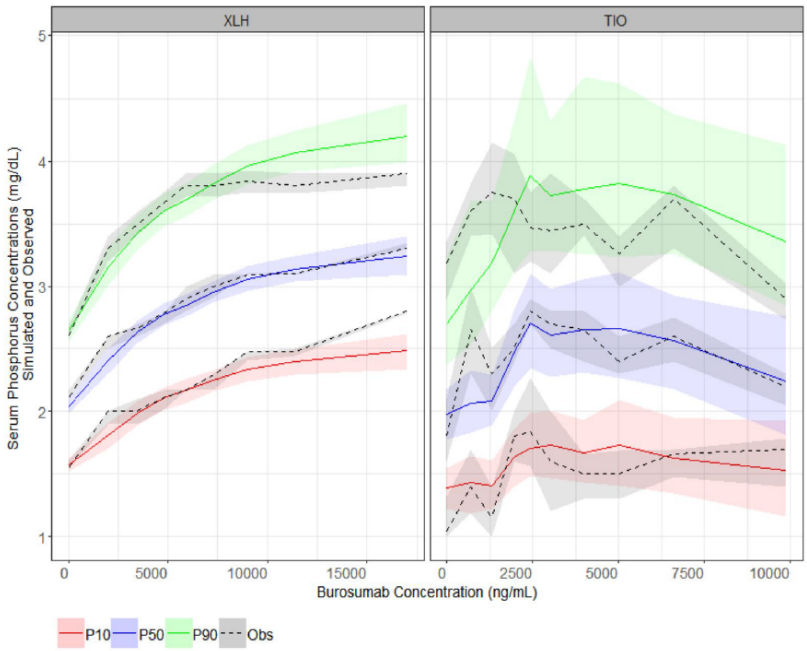
BSV= Between subject variability; CI= Confidence interval; E0= Baseline serum phosphorus; EC50= Simulated serum burosumab concentration to reach 50% of maximal effect; Emax= Maximum effect; FGF23 = Fibroblast growth factor 23 (pg/mL); PD= Pharmacodynamic; PK= Pharmacokinetic; RSE= Relative standard error; $simC_{Burosumab}$ = Simulated burosumab concentration; WT = Body weight (kg).
Note 1: The model equation is: $Phos=E_0+(Emax\times simC_{Burosumab}{}^{\gamma})/(EC50^{\gamma}+simC_{Burosumab}{}^{\gamma})$
Note 2: One subject with TIO had missing FGF23 at baseline, which was replaced by 356.1 (pg/mL).

Figure 6: Goodness-of-Fit - Final Population PK/PD Model of Serum Phosphorus



IPRED = Individual predicted serum phosphorus; LOESS = Locally weighted scatter plot smoothing; PD = Pharmacodynamic; Phosp= Phosphorus; PK= Pharmacokinetic; PRED = Population predicted serum phosphorus; TIO = Tumor-induced osteomalacia; XLH= X-linked hypophosphatemia.
Note 1: Red circles = Subjects with TIO; Black circles = Subjects with XLH.
Note 2: 6 subjects (9 observations) had |CWRES| > 4; CWRES = Conditional weighted residuals.

Figure 7: Visual Predictive Check of Burosumab Concentration/Serum Phosphorus Relationship for SC Administration of Burosumab in Subjects with TIO and XLH



Obs= Observations; P10= 10th percentile; P50= 50th percentile; P90= 90th percentiles; PD = Pharmacodynamic; PK= Pharmacokinetic; PI= Prediction interval; TIO = Tumor-induced osteomalacia; 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 10 bins with same number of samples by bin by population.
Note 3: Dashed lines represent percentiles of observed serum phosphorus levels within each bin (90th percentiles in green, 50th percentiles in blue and 10th percentiles in red); shaded area represent 95% percentile interval of percentiles of predicted concentrations (90th percentiles in green, 50th percentiles in blue and 10th percentiles in red).

Although E0 was affected by body weight with statistical significance, the magnitude of this effect was not clinically meaningful. For example, model estimated E0 values were 2.20 mg/dL and 1.79 mg/dL based on the minimum and maximum body weight values observed in the TIO studies (i.e. 36.4 kg and 150 kg, respectively), which is a moderate difference of ~20%.

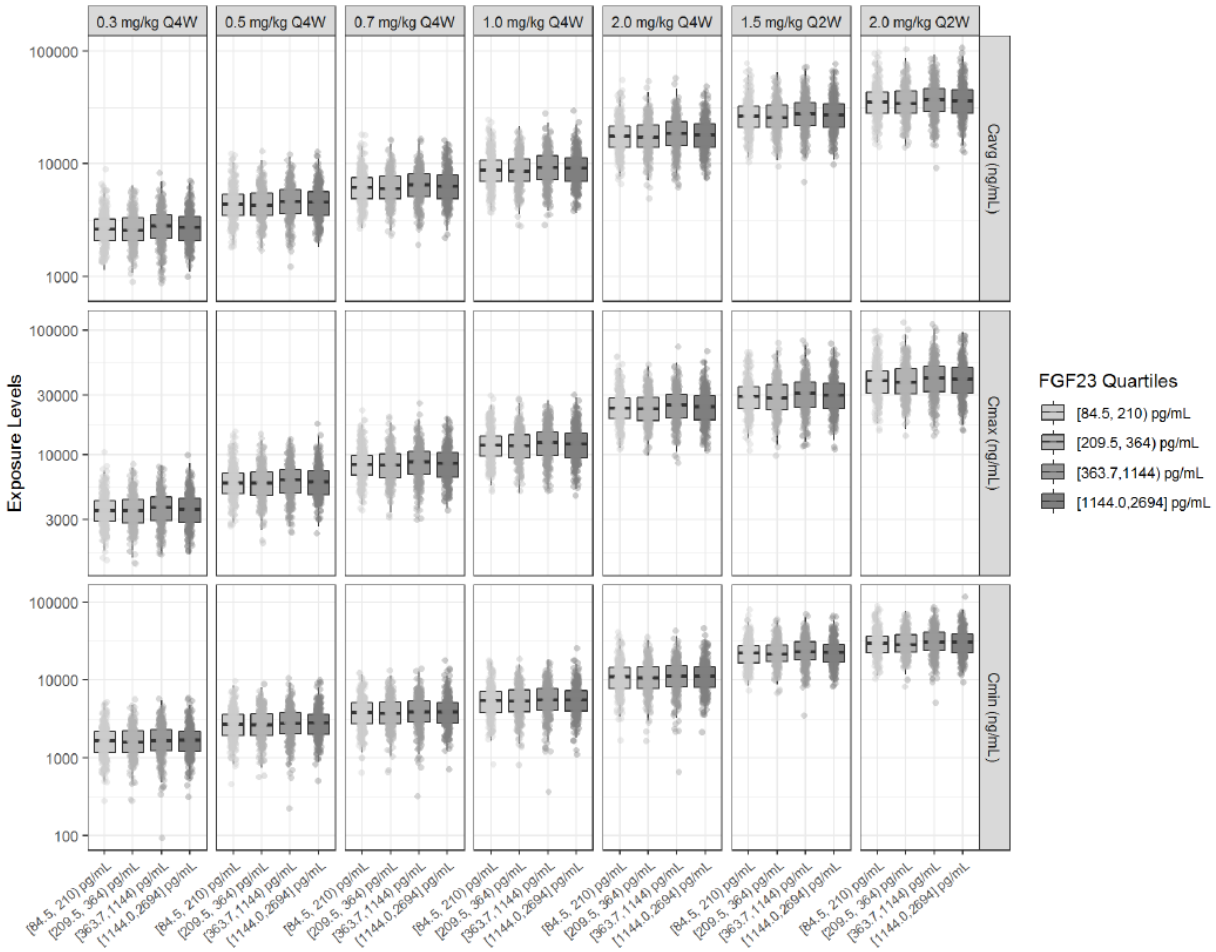
Baseline FGF23 was shown to be inversely related to E0 and directly related to EC50. Thus, serum phosphate concentrations are dependent upon FGF23 levels. Because hypophosphataemia is driven by excess FGF23 and burosumab is a specific antibody against FGF23, the above correlations between baseline FGF23 and E0/EC50 is anticipated. It appears that the on-target pharmacological potency (i.e., EC50) of burosumab is dependent on baseline FGF23 level. The model-estimated EC50 in a subject with the lowest baseline FGF23 (84.5 pg/mL) was approximately one-third compared to that in a subject with a median baseline FGF23 (356 pg/mL). Likewise, model-estimated EC50 value in a subject with the highest observed baseline FGF23 (2694 pg/mL in this study population) would be ~4-fold higher compared to that in a subject with the median baseline FGF23. Accordingly, these subjects may require higher titrated doses to achieve the desired therapeutic effects.

Monte-Carlo Simulations to Support Dosing Regimens of Burosumab in Adult Subjects with TIO

As indicated in the previous section, the dosing regimen to target a desired PD effect (i.e., normalisation of serum phosphate level) may be different in individual subjects with TIO depending on the individual baseline FGF23 levels. To explore the optimised dosing regimen in subjects with TIO, a virtual population of 1000 patients with TIO was derived from the baseline levels of body weight and FGF23 observed in adults obtained from two clinical studies (UX023T-CL201 and KRN23-002). A stratified random sampling was conducted to select TIO patients based on the observed baseline FGF23 levels by quartile groups: 84.5-210, 210-364, 64-1144 and 1144-2694 pg/mL. The population PK and PK/PD models were used to

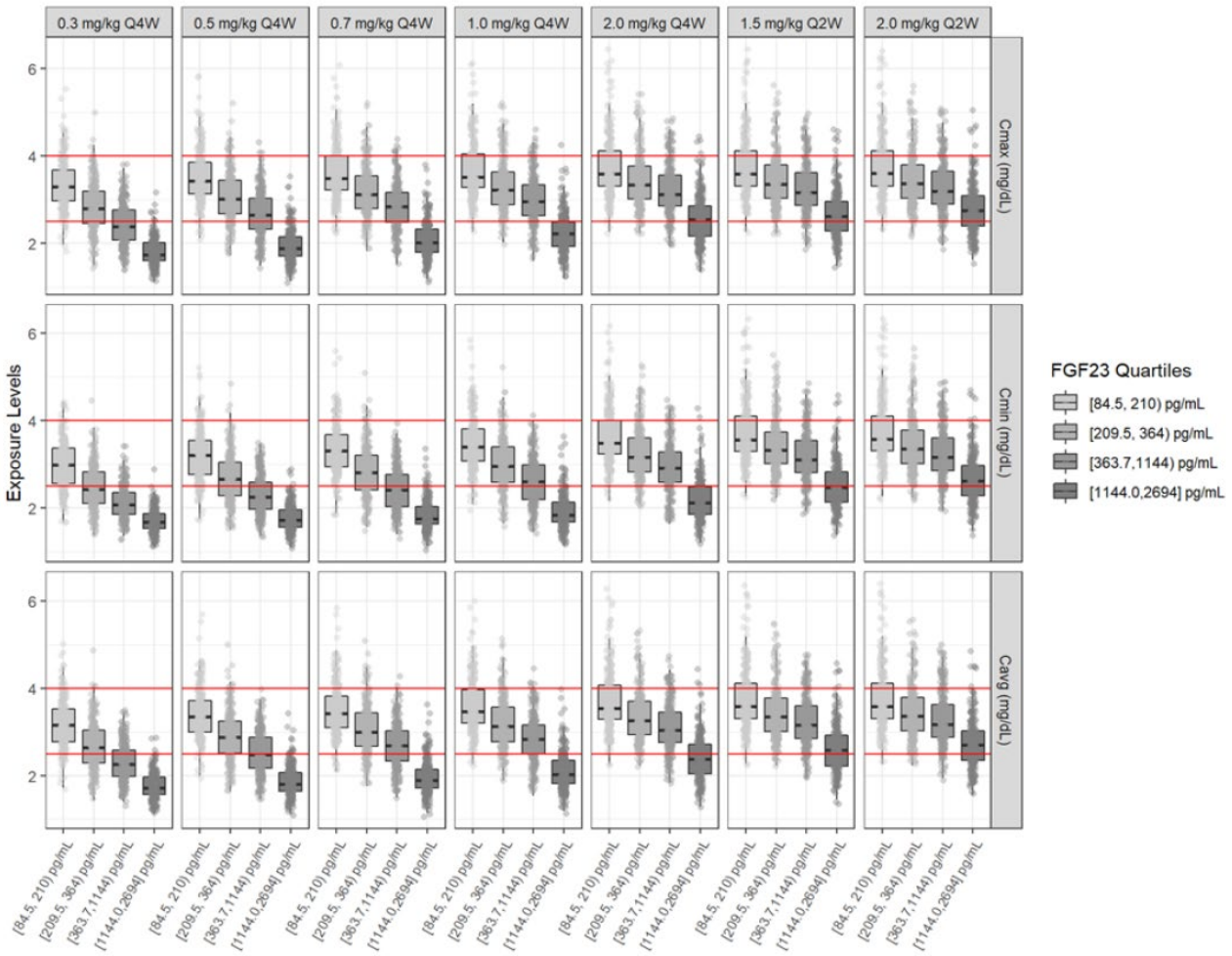
simulate steady-state serum burosumab and phosphate concentration-time profiles for five Q4W doses (0.3, 0.5, 0.7, 1.0 and 2.0 mg/kg Q4W) and two Q2W doses (1.5 and 2.0 mg/kg Q2W). Distributions of Cmin, Cmax and Cavg of burosumab concentrations and serum phosphorus levels for all dosing regimens are respectively presented in Figure 8 and Figure 9 by FGF23 categories. 1000 simulations were performed for each FGF23 quartile, i.e. 1000 PK and subsequent serum phosphorus profiles.

Figure 8: Distributions of Exposure Levels of Serum Burosumab in TIO Subjects Receiving 0.3 to 2.0 mg/kg Q4W and Q2W at Steady-State Stratified by FGF23 Groups



Cavg= Average concentration; Cmax= Maximum concentration; Cmin= Minimum concentration; FGF23 = Fibroblast growth factor 23; Q2W= Biweekly (once every two weeks); Q4W= Monthly (once every four weeks); TIO = Tumor-induced osteomalacia

Figure 9: Distributions of Serum Phosphate in Subjects with TIO at Steady-state Stratified by Baseline FGF23



C_{avg}= average concentration; C_{max} = maximum concentration; C_{min} = minimum concentration; FGF23 = fibroblast growth factor 23; Q2W= once every 2 weeks; Q4W= once every 4 weeks; TIO = tumour-induced osteomalacia.
Note: Horizontal red lines represent normal serum phosphate (i.e., 2.5-4.0 mg/dL).
Source: ULTR-PMX-BUROSUMAB-1280/TIO, Figure 16.

A 0.3 mg/kg Q4W dose of burosumab is predicted to achieve serum phosphate concentration within the normal ranges for the majority of subjects in the 1st and 2nd quartile of FGF23 (84.5 to 364 pg/mL) at Cmax and Cave and approximately 50% of subjects in the 3rd quartile of FGF23 (363.7 to 1144 pg/mL) at Cmax. The median baseline FGF23 levels across the 27 adult TIO subject enrolled in the study was 356 pg/mL, indicating that the baseline FGF23 levels for the majority of the 27 adult subjects with TIO enrolled in Studies UX023-CL201 and KRN23-002 are clustered toward the lower range. However, the model and simulations also indicate higher dose levels may be required to achieve optimal therapeutic effects for certain TIO subjects with high baseline FGF23. For example, for subjects with the baseline FGF23 in the 4th quartile (i.e., 1144 to 2694 pg/mL), the simulation results suggest that 2.0 mg/kg Q4W may still be sub-optimal and a higher dose up to 2.0 mg/kg Q2W may be necessary to achieve the desired PD effects.

Monte-Carlo Simulation to Support Dosing Regimens of Burosumab in Paediatric Subjects with TIO

The population PK and PK/PD models in adults with TIO were used to simulate the burosumab exposure and serum phosphate to support dosing regimen in paediatric patients with TIO from 1 to 17 years of

age. The distribution of body weight in paediatric subjects with TIO was assumed to be same with that in healthy paediatric subjects. This information was obtained from the growth chart maintained at the Center for Disease Control and Prevention (CDC) in the United States (CDC, 2019). Subjects were stratified across age tiers and body weights as summarised in Table 12. For the simulation, baseline serum FGF23 was fixed at 356 pg/mL, the median value in adult subjects with TIO from two clinical studies. This value was comparable to that observed from four case studies in paediatric subjects with TIO (3 to 14 years of age) available in the literature (Imel et al. 2006; Fernandez-Cooke et al. 2015). Burosumab and serum phosphate levels were simulated at steady-state conditions based on dosing regimens of 0.3, 0.4, 0.5, 0.8, 1.0, 1.5 and 2.0 mg/kg Q2W as well as 1.0, 1.5 and 2.0 mg/kg Q4W and serum phosphate levels were compared with the target interval in healthy paediatric subjects based on age groups (i.e., 3.2 to 6.5 mg/dL and 2.3 to 4.5 mg/dL for the age groups of 1 to 12 years and 13 to 17 years, respectively).

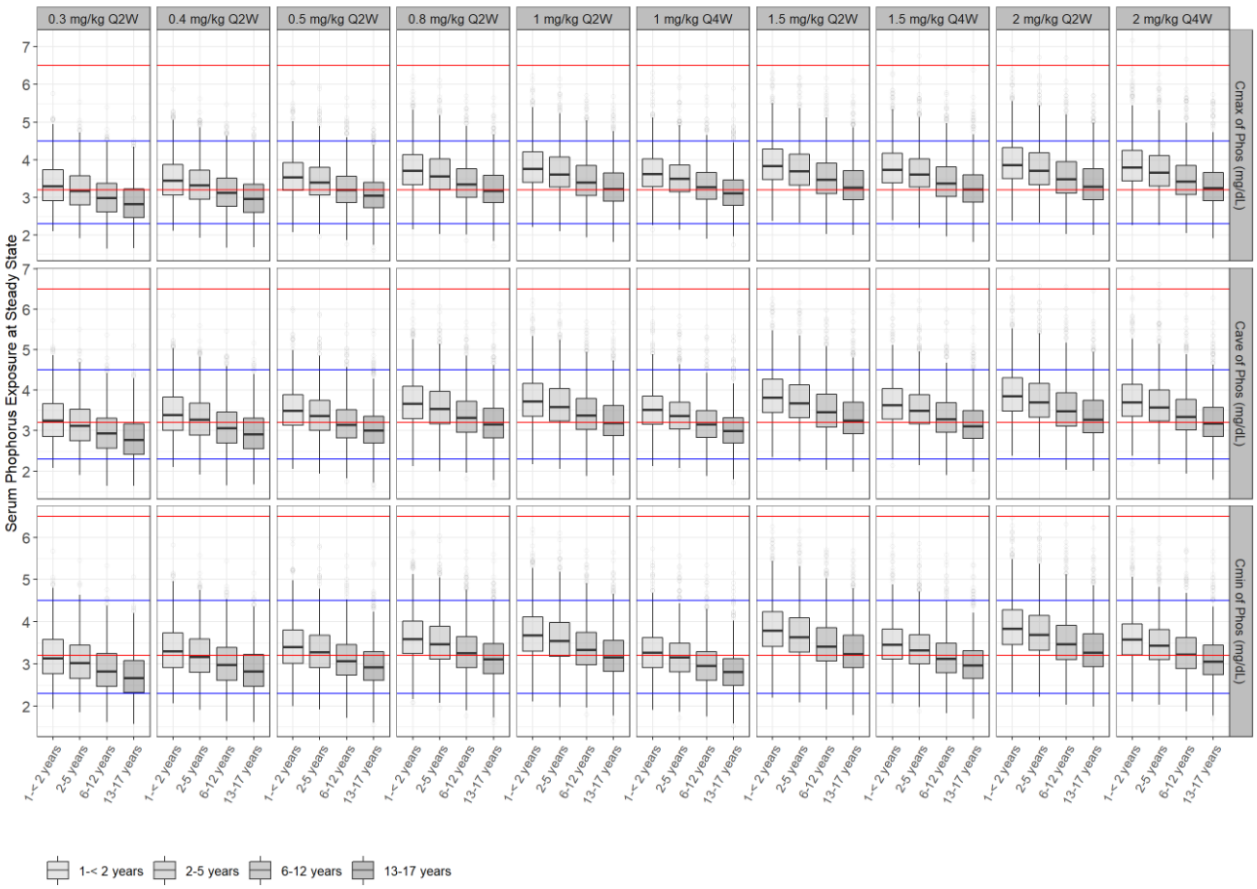
Table 12: Descriptive Statistics of Body Weight by Age Group

Mean (CV%) Median [10th – 90th percentiles]			
1-< 2 years (N=1000)	**2-5 years (N=1000)**	**6-12 years (N=1000)**	**13-17 years (N=1000)**
11.2 (13.0%) 11.1 [9.44 - 13.3]	16.9 (21.9%) 16.2 [12.7 - 21.9]	36.5 (35.3%) 33.8 [22.3 - 54.4]	64.6 (23.5%) 61.7 [47.0 - 85.1]

CV= coefficient of variation; N= number of subjects

Figure 10 summarises the predicted distribution of serum phosphate levels at Cmin, Cmax and Cavg for all dosing regimens by paediatric age groups. Distributions of body weight are presented by age group.

Figure 10: Distributions of Simulated Serum Phosphate in Paediatric Subjects with TIO at Steady-state Stratified by Age Groups



Cavg= Average concentration; Cmax= Maximum concentration; Cmin= Minimum concentration; Q2W= Biweekly (once every two weeks); Q4W= Monthly (once every four weeks); TIO = Tumor-induced osteomalacia
Note: Horizontal red lines represent target of serum phosphorus in pediatric population with TIO based on the age groups 1 to 12 years old (i.e., 3.2 – 6.5 mg/dL). Horizontal blue lines represent target of serum phosphorus in pediatric population with TIO based on the age group 13 - 17 years (i.e., 2.3 – 4.5 mg/dL).

Proportions of subjects with serum phosphorus outside the normal range in paediatric population within each age group were computed for all dosing levels (Table 13).

Table 13 Percentages of Subjects with Simulated Serum Phosphorus Outside the Normal Range by Dose Levels and Age Groups

Arms	Serum Phosphorus Parameters	Normal Range 3.2 – 6.5 mg/dL for 1 to 12 years old 2.3 – 4.5 mg/dL for 13 to 17 years old			
		1 - < 2 years	2-5 years	6-12 years	13-17 years
0.3 mg/kg Q2W	Cmax>ULN	0%	0%	0%	0.2%
	Cmin<LLN	53.7%	60.4%	72.9%	24.2%
	Cavg<LLN	47.4%	54.6%	66.8%	17.5%
0.4 mg/kg Q2W	Cmax>ULN	0%	0%	0%	1.0%
	Cmin<LLN	44.7%	51.8%	63.7%	15.0%
	Cavg<LLN	38.7%	45.6%	59.1%	10.7%
0.5 mg/kg Q2W	Cmax>ULN	0%	0%	0%	1.6%
	Cmin<LLN	36.8%	43.8%	59.8%	10.5%
	Cavg<LLN	30.2%	37.8%	53.5%	7.3%
0.8 mg/kg Q2W	Cmax>ULN	0%	0%	0%	3.1%
	Cmin<LLN	22.1%	29.8%	45.1%	4.4%
	Cavg<LLN	18.5%	26.6%	41.4%	3.1%
1.0 mg/kg Q2W	Cmax>ULN	0%	0%	0%	4.0%
	Cmin<LLN	18.2%	25.9%	40.8%	2.8%
	Cavg<LLN	14.8%	22.9%	37.7%	2.6%
1.5 mg/kg Q2W	Cmax>ULN	0%	0%	0%	5.6%
	Cmin<LLN	12.9%	19.7%	35.3%	2.2%
	Cavg<LLN	11.8%	17.9%	33.4%	1.9%
2.0 mg/kg Q2W	Cmax>ULN	0.1%	0.1%	0%	6.7%
	Cmin<LLN	11.5%	17.4%	32.5%	1.9%
	Cavg<LLN	11.2%	17.1%	31.3%	1.8%
1.0 mg/kg Q4W	Cmax>ULN	0%	0%	0%	1.9%
	Cmin<LLN	45.3%	53.5%	69.1%	15.7%
	Cavg<LLN	28.0%	36.1%	53.7%	6.4%
1.5 mg/kg Q4W	Cmax>ULN	0.1%	0.1%	0%	3.2%
	Cmin<LLN	31.8%	40.3%	56.7%	9.0%
	Cavg<LLN	19.9%	27.6%	44.6%	3.3%
2.0 mg/kg Q4W	Cmax>ULN	0%	0%	0.1%	4.3%
	Cmin<LLN	24.5%	32.2%	49.0%	5.3%
	Cavg<LLN	15.3%	22.1%	40.5%	1.8%

Cavg= Average concentration; Cmax= Maximum concentration; Cmin= Minimum concentration; LLN = lower limit of normal; Q2W= Biweekly (once every two weeks); Q4W= Monthly (once every four weeks); TIO = Tumor-induced osteomalacia; ULN = upper limit of normal

Note: Serum phosphorus in pediatric population with TIO were compared to the normal range within each age group (i.e., 3.2 – 6.5 mg/dL and 2.3 – 4.5 mg/dL for the age groups of 1 to 12 years and 13 to 17 years, respectively).

The dose of 0.4 mg/kg Q2W predicted to result in a proportion of paediatric TIO patients reaching normal serum phosphate levels. Approximately 55 to 36 to percent of TIO patients from 1 to 12 years of age, respectively and 85 percent of TIO patients from ages 13 to 17 are predicted to reach serum phosphate levels above the lower limit of normal at Cmin (3.2 and 2.3 mg/dL, respectively). In addition, the modeling simulations predict that no subjects from the ages ranging from 1 to 12 years of age and only 1% of adolescent patients ranging from the 13 to 17 years of age are predicted to achieve serum phosphate levels above the upper limit of normal at Cmax (6.5 and 4.5 mg/dL, respectively). The dosing regimen up to 2.0 mg/kg Q2W (the highest dose simulated) appears to be safe, considering no hyperphosphatemia was projected in pediatric TIO patients ages 1 to 12 years of age and < 7% of adolescent TIO patient ages 13 to 17 year of age are predicted to reach serum phosphate levels above the upper limit of normal.

2.3.5. Discussion on clinical pharmacology

Individual dosing of Crysvita is based on titration to maintain normal serum phosphorus levels. In both TIO clinical trials the starting dose was 0.3 mg/kg. In Study UX023T-CL201, the median dose was 0.9 mg/kg at Week 48, and in Study KRN23-002, 0.8 mg/kg at Week 48.

Bioanalytical methods

With the exception of the update to the ADA assay, all other assays used for sample analysis have been described in previous submissions. An ECL assay is used for screening patient samples for ADA. There are two versions of this assay, based on the same principles, but performed at different laboratories. Full details of the first method were previously submitted in procedure EMEA/H/C/004275/II/0010/G. This assay was used to evaluate ADA samples in clinical study UX023T-CL201. Within the current type II variation, data has been presented for a second assay, which was used to screen patient samples in clinical study KRN23-002.

The second ECL method has been validated in line with the general principles of the Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev1). The method is sufficiently sensitive and is not subject to any apparent hook effect. Selectivity was evaluated in healthy, haemolytic and hyperlipidemic samples and no interference was observed at the low positive control level of 100 ng/ml. Data to support selectivity in relevant patient population was provided. The method demonstrated increased drug tolerance when compared to the first method. The MAH has justified the demonstration of tolerance using a single run on the basis of the precision and robustness of the method. While, it would be usual to see multiple runs performed for evaluation of drug tolerance, it is acknowledged that the method has good precision. The precision of the screening and confirmatory assays and the reproducibility of the titration assay are acceptable. The cut point determination follows a standard approach and is, generally, acceptable. The procedure for exclusion of outliers is described and is acceptable. However, it is noted that healthy patients were used to derive the cut point. The MAH justified the use of the healthy subject cutpoint in the ADA analysis of samples from study KRN23-002 by the very limited availability of sample from TIO patients and the similarity in signal between the pre-study validation in healthy subjects and pre-dose samples from study KRN23-002, which is acceptable. During the study, the stability of the reagents and the control samples was assessed by monitoring the results of control samples in each run. The stability of reagents and control samples was verified since control samples in each assay run met the acceptance criteria. For samples stored at or below – 20 °C, the stability of ADA is generally accepted so the absence of specific stability data will not be queried.

Appropriate run acceptance criteria are defined for the method. During validation, the control samples in each assay run met the acceptance criteria and the CV of duplicate ECL signals was less than 30% across runs. The mean and standard deviation of response ratios of control LPC samples across all the assay runs were calculated to determine the lower limit for LPC. The lower limit for the ECL response ratio of LPC samples was calculated as 1.53 which is consistent with a 1% assay failure rate. The positive control antibody was suitably qualified.

For study UX023T-CL201, out of 139 samples analysed, one sample had an inconclusive ADA result and nine samples had a result of "unknown". Since all eight subjects involved had multiple additional ADA samples collected and reported, it is unlikely that these ten samples affected the subjects ADA status. This rationale is agreed. For study KRN23-002, all study samples contained burosumab below the drug tolerance threshold of the assay. The response is acceptable.

Population PK analysis

A population PK analysis, with pooled TIO and XLH PK data, have been used to describe PK in the TIO patient population. Due to the limited TIO sample size the pooled analysis approach is adequate. The final

population PK model described the TIO data well and no differences were detected between the two patient populations. In adult subjects with TIO having a median body weight of 76 kg, CL/F and V/F of burosumab were projected to be 0.305 L/day and 8.03 L, respectively. Corresponding elimination $t_{1/2}$ was projected to be ~18 days. There was no indication that baseline FGF23 affect the burosumab serum concentration, despite the higher baseline FGF23 values in the TIO population. Shrinkage values for V/F and CL/F, in the TIO population, were estimated to 9.36% and 25.0%, respectively. It is agreed that the values are sufficiently low to derive adequate individual PK parameters.

Population PKPD analysis

A pooled analysis approach was also used for the PKPD model of the relationship between serum phosphorus levels and the burosumab serum concentration. The final PKPD model describes the relationship between serum phosphorus levels and burosumab serum concentration well and is considered adequate. Shrinkage estimates for E0, Emax and EC50 were 44.3%, 31.8% and 7.81%, respectively. The shrinkage values for E0 and Emax indicate that the derived individual E0 and Emax parameters will be somewhat shrunk towards the population mean values. It is agreed that the due to the small study size greater shrinkage estimates are expected, however when interpreting the PD predictions, it should be kept in mind that the variability will be somewhat under predicted.

The main difference between the two patient populations is the effect of baseline FGF23 on the response (covariate on both E0 and EC50) detected for the TIO population, as well as and a somewhat lower EC50 value. Although the TIO sample size is small and covariate effects should be interpreted with caution, the inclusion of FGF23 as a covariate clearly improved the prediction of the phosphorus levels it the TIO population. Patients with FGF23 levels at baseline > 2000 pg/mL (N=3) seem to require a high dose; however, no trend is visible for patients with FGF23 levels at baseline < 2000 pg/mL. Thus, it is agreed that there is no clear relationship between baseline FGF23 levels and final dose. Subsequently there is not sufficient evidence to adjust the starting dose based on the baseline FGF23 value.

Dosing simulations in adult subjects with TIO

The final popPK and PKPD models were used to simulate burosumab and phosphorus serum concentrations given seven different dosing regimens. Resampling of subject's characteristics from the actual TIO clinical trials, preformed based on quartiles of baseline levels of FGF23 were used.

The simulated burosumab serum levels for 2.0 mg/kg Q2W display markedly higher exposure levels (median Cmax ~40000 ng/mL) than have been previously studied in the XLH population (95th percentile of Cmax 16882 ng/mL for 1.0 mg/kg Q4W). Furthermore, the proposed maximum total dose is 180 mg, compared to the previously 90 mg maximum dose for the XLH population. The MAH has clarified that the maximum total dose of 180 mg was not implemented in the initial PK. Thus, new simulations and subsequent exposure predictions have been provided. As expected, a slightly lower exposure range was presented. Furthermore, the exposure range given a 2.0 mg/kg Q2W dose (maximum 90 mg) in the adolescent XLH population was presented. Compared to the proposed dosing regimen for the adolescent TIO population (the only difference is the maximum dose of 90 mg vs 180 mg) the exposure range in TIO population is somewhat higher (as expected). The MAH has provided the requested comparison, nonetheless, it is not clear why it would be acceptable to have a maximum dose of 180 mg in the TIO population but not in the XLH population. The inconsistency between the maximum recommended dose between TIO and XLH adult patient populations are further addressed in the Safety section.

The results of the PKPD simulations clearly visualize that it is the baseline FGF23 levels that are predictive of the response rather than the exposure levels. However, due to the limited input on demographics and FGF23 levels, the results of the simulations should be interpreted with caution.

It is noted that the proposed starting dose in TIO patients (0.3 mg/kg) is lower than the recommended starting dose for XLH patients (1 mg/kg), which is somewhat counter-intuitive given the observed higher

FGF23 levels in the TIO population. However, as several TIO patients remained on the 0.3 mg/kg dose level after the titration phase the starting dose can be accepted.

Dosing simulations in paediatric subjects with TIO

No data are available in paediatric patients with TIO. Therefore, age-extrapolated simulations using the popPK and PK/PD models developed for adults with TIO were conducted to select a dosing regimen for paediatric patients (full-extrapolation approach).

The extrapolation is based on the assumption of similar PK and PD properties of burosumab between paediatric and adult patients with TIO. Similar PK and PD properties of burosumab were found between paediatric and adult patients with XLH. Similar PK properties of burosumab were found between adult XLH and TIO subjects in the population PK analysis. Due to the common pathologic cause, the applicant contends a high likelihood exists that the PD properties of burosumab are similar in paediatric and adult subjects with TIO. The extreme rareness of TIO in paediatric patients unable to undergo tumour resection is acknowledged, as is the difficulty in obtaining sufficient data in this population to draw firm conclusions. Population PK/PD modelling indicated that the exposure/response relationships across adult and paediatric subjects with XLH were similar; neither age nor FGF23 levels were identified as significant covariates. Thus, the MAH has provided an adequate discussion and justification as to why it is reasonable to assume that the PK/PD of burosumab would be similar in paediatric patients to that in adult patients with TIO. It is agreed that any differences in the PD relationship between adults and paediatrics is likely to be captured by the proposed weight-based posology of burosumab. Further, incremental dose adjustments of burosumab are proposed to normalise serum phosphate levels as needed.

The simulations were based on the population PK and PKPD models with the model parameters for the TIO population, however some clarification on the simulations was sought during the procedure. A paediatric weight distribution was simulated based on the CDC weight distributions for 1 to 17 years of age. 1000 virtual patients were simulated for each age group, which is accepted. However, the simulations for the paediatric TIO population assumed that all patients had a baseline FGF23 value of 356 pg/mL. The assumption of a fixed baseline FGF23 value is a major assumption since baseline FGF23 is the major predictor for the response. As such the simulated phosphorus levels to support the dosing regimen in children are of limited value. FGF23 levels varied widely in adults and the simulations were stratified FGF23 quartiles. To evaluate the impact of baseline FGF23 levels on the PK and E/R relationship of burosumab in paediatric TIO patients (aged 1-17 years), the MAH performed additional PK and PK/PD simulations. Given the limited information on the range of FGF23 levels in paediatric TIO patients, it is acceptable that the MAH based the distribution of levels observed in adult TIO patients.

Based on the results of the simulation exercise, the selected starting dose for paediatric patients (1-17 years) is 0.4 mg/kg Q2W. At this dose, ~85% of adolescents are predicted to achieve serum phosphate levels above the lower limit and 1% predicted to achieve levels above the maximum level. At the lower dose of 0.3 mg/kg Q2W, ~75% of adolescents are predicted to achieve phosphate levels above the lower limit with only 0.2% predicted to achieve levels above the maximum level. Additional simulations support a starting dose of 0.3 mg/kg Q2W for adolescent patients (aged 13-17 years), with incremental dose adjustments as required.

In the younger age groups (1-12 years), there is no predicted risk of hyperphosphataemia at 0.4 mg/kg Q2W, but the majority of subjects will likely need a higher dose to normalise serum phosphate. At the maximum tested dose of 2 mg/kg Q2W, the risk of hyperphosphataemia is negligible (0-0.1%), but the majority of patients will achieve normal serum phosphate levels. Although it seems that higher starting doses might be appropriate in children aged 1-12 years, the proposed conservative starting dose of 0.4 mg/kg Q2W in this age group, with incremental dose adjustments as required, is accepted since it minimises the risk of developing hyperphosphataemia.

The simulations suggest that for the age ranges of 1 to 12 years of age, dose levels of burosumab required to normalize serum phosphorous levels may increase with age. The MAH has agreed that a lower starting dose of 0.3 mg/kg Q2W burosumab for adolescent TIO patients (aged 13-17 years) is more appropriate than the previously proposed higher starting dose.

The simulated distribution of burosumab serum concentration in the paediatric TIO population has not been presented. However, as the baseline FGF23 value does not affect the burosumab exposure and that the PK properties between TIO and XLH patients are similar, the burosumab serum concentrations are expected to be similar in the paediatric TIO population as in the paediatric XLH population where the proposed dosing regimen has been accepted.

Overall, the dosing recommendation in the TIO population is in general similar to the dosing recommendation previously accepted for the XLH population, and as such the burosumab exposure is expected to be similar. The exception is the 2.0 mg/kg Q2W dosing strategy, with maximum dose of 180 mg, in adults. A 2.0 mg/kg Q2W, maximum dose 90 mg, dosing regimen has previously been accepted in the paediatric XLH population. The PKPD modelling results indicate that increased baseline levels of FGF23 could require an increased dose to achieve normal phosphorus levels, which seems reasonable due to the increase in target levels. However, due to the small sample size of TIO patients the relationship between burosumab exposure and phosphorus levels for high baseline FGF23 levels as well as high dose levels are based on an extremely small sample and should be interpreted with caution. Similarly, the simulation results for the paediatric population should be interpreted with caution. Nonetheless, given careful titration of the dose based on phosphorus levels, the proposed dosing regimen is considered acceptable

2.3.6. Conclusions on clinical pharmacology

The burosumab pharmacokinetics and PKPD have been adequately described in the adult TIO population. Due to the small sample size of TIO patients the relationship between burosumab exposure and phosphorus levels for high baseline FGF23 levels as well as high dose levels are based on an extremely small sample and should be interpreted with caution. Given careful titration of the dose based on phosphorus levels, the dosing recommendation in adult and paediatric TIO patients is accepted.

2.4. Clinical efficacy

2.4.1. Main studies

The application is based on two ongoing Phase 2-studies.

Title of Studies

UX023T-CL201: A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23, an Antibody to FGF23, in Subjects with Tumor-Induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS)-Associated Osteomalacia

KRN23-002: A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23 in Patients with Tumor-Induced Osteomalacia or Epidermal Nevus Syndrome

Methods

Study design

UX023T-CL201

Study UX023T-CL201 is an ongoing, open-label, single arm, multicentre, Phase 2 study designed to assess the efficacy, safety, pharmacokinetics (PK), and PD of burosumab in adult subjects with TIO or ENS-associated osteomalacia.

Study UX023T-CL201 includes an initial 48-week Treatment Period followed by a Treatment Extension Period for a total treatment duration of up to 300 weeks or until 31 Jan 2021 (per Protocol Amendment 6 after the data cut-off for the Week 144 CSR), whichever is sooner, or until one of the following occurs: the study drug is commercially available in the subject's local territory, the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the Investigator or the Sponsor, or the study is terminated.
A Safety Follow-up Period of up to 12 weeks from the last dose of study drug is also included.

Efficacy and safety data are presented through 144 weeks of treatment. The study is ongoing as of the data cut-off date for the Week 144 CSR (11 Jan 2019).

KRN23-002

Study KRN23-002 is an ongoing, open-label, multicentre, Phase 2 study designed to assess the efficacy, safety, PK and PD of burosumab in adult subjects with TIO or ENS-associated osteomalacia.

The planned treatment is 144 weeks or until one of the following occurs: the study drug is commercially available in the subject's local territory, the subject withdraws consent and discontinues from the study, the subject is discontinued from the study at the discretion of the Investigator or the Sponsor, or the study is terminated. The study was ongoing as of the data cut-off date for Week 88 CSR (03 May 2018).

Study participants

UX023T-CL201

This study is being conducted at eight centres in the US.

Key Inclusion Criteria

- A clinical diagnosis of TIO/ENS-associated osteomalacia based on evidence of excessive FGF23 that was not amenable to cure by surgical excision of the underlying tumour/lesion (documented by Investigator).
- ≥ 18 years of age.
- Fasting serum phosphorus level < 2.5 mg/dL (<0.81 mmol/l).
- FGF23 level ≥ 100 pg/mL by Kainos assay.
- TmP/GFR < 2.5 mg/dL.
- An estimated glomerular filtration rate (eGFR) ≥ 60 mL/min (using Cockcroft-Gault formula). Subjects with an eGFR ≥ 30 but < 60 mL/min were considered eligible as long as, in the opinion of the Investigator, the decline in renal function was not related to nephrocalcinosis.
- Had a corrected serum calcium level < 10.8 mg/dL (<2.7 mmol/L).

Exclusion Criteria

- A prior diagnosis of human immunodeficiency virus, hepatitis B, and/or hepatitis C.
- A history of recurrent infection, a predisposition to infection, or a known immunodeficiency.
- Was pregnant or breastfeeding at Screening or was planning to become pregnant (self or partner) at any time during the study.
- Had participated in an investigational drug or device trial within 30 days prior to Screening or was currently enrolled in another study of an investigational product or device.
- Had used a therapeutic mAb, including burosumab, within 90 days prior to Screening, or had a history of allergic or anaphylactic reactions to any mAb.
- Had a history of any hypersensitivity to burosumab excipients that, in the judgment of the Investigator, placed the subject at increased risk for adverse effects.
- Had used a pharmacologic vitamin D metabolite or its analogue (eg, calcitriol, doxercalciferol, and paricalcitol), phosphate, or aluminium hydroxide antacids within 2 weeks prior to Screening or during the study.
- Had used medication to suppress PTH (eg, Sensipar, cinacalcet, calcimimetics) within 2 months prior to Screening.
- Had a history of malignancy within 5 years of study entry with the exception of phosphaturic mesenchymal tumors (PMTs) of the mixed connective tissue type or non-melanoma skin cancers such as basal cell skin cancer
- Had donated blood or blood products within 60 days prior to Screening.
- Had a history of allergic reaction to or had shown adverse reactions to tetracycline (eg, tetracycline HCl and demeclocycline), benzodiazepines, fentanyl, or lidocaine.
- Had any condition, which in the opinion of the Investigator and Sponsor, could present a concern for either subject safety or difficulty with data interpretation

KRN23-002

This study was conducted at four sites in Japan and three sites in South Korea.

The eligibility criteria in KRN23-002 were largely identical to those of Study UX023T-CL201.

Treatments

UX023T-CL201

All subjects received SC burosumab treatment at a starting dose of 0.3 mg/kg every fourth week (Q4W). Doses were then titrated at Weeks 4, 8, 12, and 16 to achieve a fasting peak serum phosphorus level within the target range of 2.5 to 4.0 mg/dL (0.8 – 1.3 mmol/L). Titration was allowed to continue beyond the Week 16 visit if needed to achieve a dose that optimized trough serum phosphorus levels to within the normal range, to a maximum dose of 2.0 mg/kg Q2W.

Although the maximum dose administered to date in clinical studies in adults with XLH is 1.0 mg/kg Q4W, the maximum dose selected in this study is 2.0 mg/kg Q2W. This dose was selected because it is anticipated that doses > 1.0 mg/kg may be needed to bring serum phosphorus levels up to the lower end of the normal range in subjects with TIO. Compared to subjects with XLH, FGF23 levels are higher in

subjects with TIO and ENS-associated osteomalacia, and the associated hypophosphatemia is more severe.

KRN23-002

As for Study UX023T-CL201, the starting dose was 0.3 mg/kg Q4W with the same dose titration schedule. As opposed to Study UX023T-CL201, the maximum dose in-KRN23-002 was 2 mg/kg Q4W instead of 2 mg/kg Q2W.

For subjects in Japan, self-administration of burosumab was allowable in hospital or at home at or after Week 48.

Objectives

UX023T-CL201

The primary objectives of Study UX023T-CL201 were to establish the effect of burosumab treatment on increasing serum phosphorus levels in adults with TIO and to establish the change from Baseline in histomorphometric indices by analysis of iliac crest bone biopsies.

The secondary efficacy objectives evaluated burosumab treatment effect on key biochemical and clinical disease parameters and symptoms in TIO, including markers of phosphate homeostasis and skeletal health, functional mobility and strength, patient-reported pain, fatigue, and health-related quality of life (HRQoL).

KRN23-002

The study objectives in Study KRN23-002 were to evaluate the efficacy and safety of KRN23 after its 144-week once every 4 weeks (Q4W) repeated subcutaneous (SC) administration to Japanese and Korean patients with TIO or ENS.

Outcomes/endpoints

UX023T-CL201

Primary endpoints

There were two co-primary endpoints in this study:

- 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 (2 weeks after dosing), as averaged across dose cycles between Baseline and Week 24.
- The change from Baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of KRN23 treatment using the following histomorphometric indices
    - O.Th
    - OS/BS
    - OV/BV
    - Mineralization lag time

Secondary Endpoints

Secondary endpoints included additional measures to assess serum phosphate levels over time, as well as the following:

- Change from baseline over time in serum FGF23, alkaline phosphatase (ALP), 1,25-dihydroxyvitamin D (1,25(OH)2D); and urinary phosphate, tubular reabsorption of phosphate (TRP), TmP/GFR, and fractional excretion of phosphate.
- Change and percent change from baseline over time in serum biochemical markers of bone turnover, including bone-specific alkaline phosphatase (BALP), carboxy terminal cross-linked telopeptide of type 1 collagen (CTx), procollagen type 1 N-pro-peptide (P1NP) and osteocalcin.
- Change from baseline in muscle strength assessed by hand-held dynamometry (HHD), Sit-to-Stand (STS) test, weighted arm lift test (WAL), and 6-Minute Walk Test (6MWT).
- Change from baseline in Brief Pain Inventory-Short Form, Brief Fatigue Inventory, and the 36-item Short Form Health Survey, version 2 (SF-36v2) over time.

KRN23-002

Primary endpoint

- Serum phosphate concentration at each test time point

Secondary endpoints

Secondary endpoints included additional measures to assess serum phosphate levels over time, as well as the following:

- Percentage changes from baseline in histomorphological parameters (O.Th, OS/BS, OV/BV and MLt) as measured at Week 48.
- Changes from baseline over time in serum FGF23, ALP, and 1,25(OH)2D, and urine phosphate, TRP and TmP/GFR.
- Changes from baseline over time in serum bone biomarkers (CTx, P1NP, BALP and osteocalcin).
- Changes from baseline over time in motor functions (HHD, STS, WAL and 6MWT).
- Changes from baseline over time in patient-reported outcomes (BPI, BFI and SF-36).

Specific methodology

Trans-iliac crest bone biopsy

In Study UX023T-CL201, to assess osteomalacia, subjects underwent iliac crest bone biopsies at baseline and Week 48. In Study KRN23-002, bone biopsies were an optional procedure.

Bone biopsy histomorphometry was interpreted centrally by trained personnel who were blinded to other subject data (Insogna et al. 2019). Specific histomorphometric parameters chosen to evaluate changes in osteomalacia with burosumab treatment include Osteoid thickness (O.Th), osteoid surface/bone surface (OS/BS), and osteoid volume/bone volume (OV/BV), which are static parameters providing information about the amount of unmineralized bone (Dempster et al. 2013). In addition, mineralization lag time (Mlt), a dynamic modelling parameter representing the mean time interval between the formation of osteoid and its subsequent mineralization (Dempster et al. 2013), was evaluated.

Bone biopsies were read centrally by a reader who was blinded to the timing of the biopsy relative to treatment.

Mineralization defects can prevent evaluation of Mlt due to very low tetracycline label uptake in the biopsies; when unavailable, Mlt was calculated using an established imputation technique. In 8 subjects in the TIO Analysis Set, in whom Mlt was not measurable, Mlt was calculated using an established imputation technique (Dempster et al. 2013).

Bone Fractures and Pseudofractures

Fractures and pseudofractures were assessed as exploratory endpoints in both TIO studies by two complementary methods: whole body bone scans, using 99mTc-labeled methylene diphosphonate, and standard radiographs (skeletal survey).

The MAH has provided a Bone Scan White Paper (not included in this report for the sake of conciseness) which provides a comprehensive critical evaluation of the assessment of fracture healing in patients with TIO treated with burosumab.

In brief summary, bone scans are highly sensitive in the detection of mineralising lesions of any size, with increased uptake at sites of injury and ongoing repair. Low specificity is an inbuilt methodological price of the high sensitivity of bone scans. Healing of a known fracture is indicated by the resolution of tracer uptake at a previously identified fracture site over time. As a result of the sensitivity of the method, complete healing as assessed by bone scan can take 2 to 3 years to show; healing can be further delayed in the presence of osteomalacia (Brenner et al. 2012; Wong et al. 2013; Matin 1979).

Bone scans on treatment were compared to baseline scans by a central reader who was blinded to subject data

Identification of fractures/pseudofractures on standard radiographs, x-ray, is dependent on the technique/angles of the images. Proper positioning of the anatomic area of interest is essential and impacts the ability to capture underlying pathology. Radiography is limited in the assessment of certain conditions such as undisplaced acute fractures or pseudofractures, which can be radiographically occult. Healing on radiographs is indicated by the presence of bridging at a fracture site, and complete healing as assessed radiographically typically occurs within 12 to 24 weeks.

A skeletal survey was conducted at Screening, including standard radiographs of multiple predefined anatomic sites including both standardised sites and sites identified on body scan or clinical observations. Skeletal surveys were read by three central readers, blinded to subject data, without adjudication. Radiographs were interpreted locally for the identification of new abnormalities and assessed centrally for changes over time; there was no communication from central readers to local sites. Follow-up radiographs of fractures were performed only if the local radiologist identified a fracture. Therefore, systematic and consistent prospective follow-up of fractures identified centrally at baseline is not available. However, this is not considered to be a major deficit in the assessment of skeletal health. Fractures only identified at baseline through a skeletal survey (and not identified by the patients' physician) are likely minimally symptomatic and not interfering with mobility. A subsequent skeletal survey was performed at Week 144 or end of study.

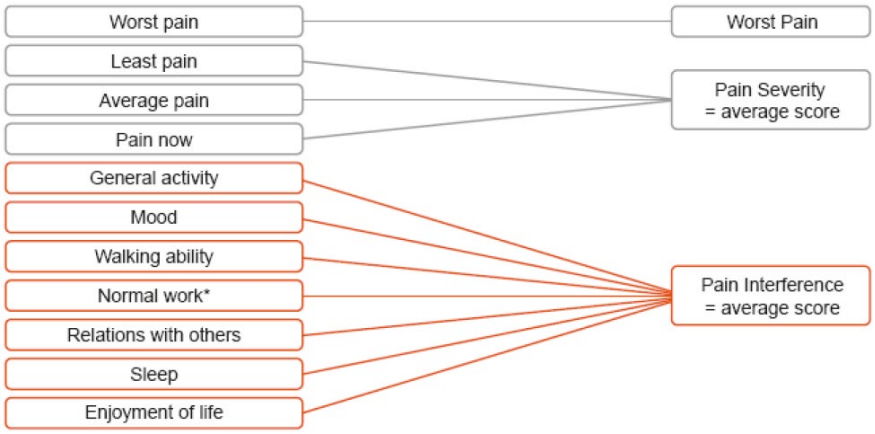
Pain, Fatigue, and HRQoL at Study Baseline

Three patient-reported scales were used to evaluate pain, fatigue and quality of Life (HRQoL): Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI) and SF-36v2. The three scales have been evaluated for relevance in adult TIO and assessed for validity, reliability and sensitivity to change in a Patient-reported Outcomes Dossier for Patients with Tumour-induced Osteomalacia, provided by the MAH.

Subjects were required not to have pharmacological vitamin D metabolite or an analogue, or oral phosphate in the 2 weeks prior to the screening visit (Week -4). The patient-reported outcomes (PRO) and functional performance assessments were taken on baseline Day -2. Therefore, TIO subjects were without treatment for approximately 6 weeks before baseline assessments. It is possible that a gap in an effective treatment could worsen physical performance and reported HRQL at baseline.

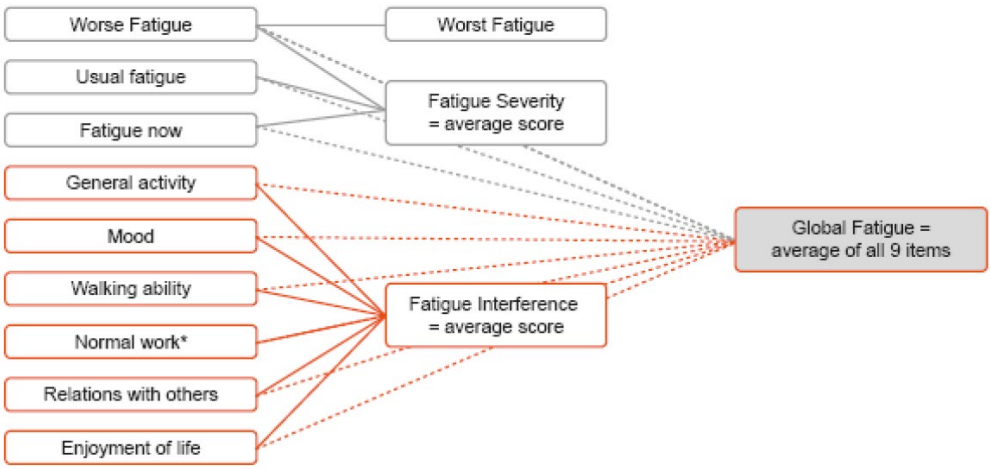
The BPI is a self-reported, pain-specific questionnaire with a recall period of 24 hours. Four of the items in the BPI evaluate pain severity and seven evaluate the interference of pain with daily life (Figure 11). Mild pain is defined as a score of 1 to 4, moderate pain is defined as a score of 5 to 6, and severe pain is defined as a score of 7 to 10 (Serlin et al. 1995).

Figure 11: Conceptual framework of the nine-time short-form BPI used in the phase 2 studies



The BFI is a self-reported questionnaire consisting of nine items related to fatigue that are rated on a 0 to 10 numerical rating scale with a recall period of 24 hours. Three items relate to the severity of fatigue now, usually and at its worse. A further six items relate to the interference of fatigue with daily functioning All nine BFI items combine together to form a global fatigue score (Figure 12).

Figure 12: Conceptual framework of the BFI

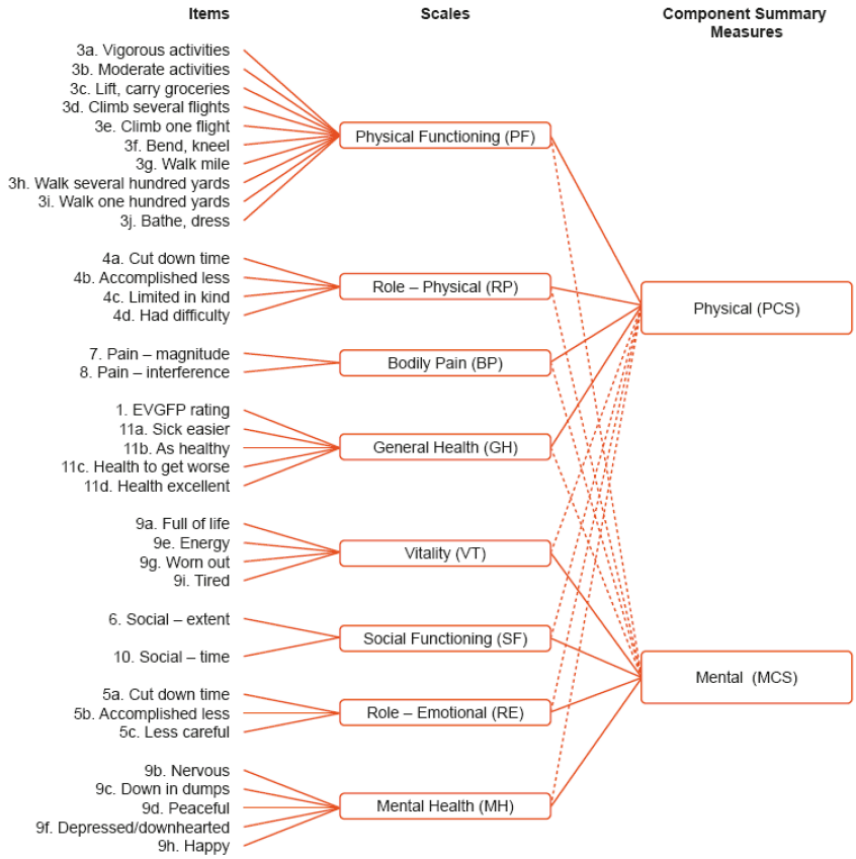


HRQoL was assessed using the SF-36v2 questionnaire. The 36 items of the SF-36 are grouped into eight domain scales, with differing numbers of contributory items, which are used to calculate Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores (Figure 7). The recall period is the last 4 weeks.

T-based scoring is used for the SF-36, standardized using the means and SD from a US general population (UX023-CL201) or a Japanese general population (KRN23-002). The T-based scores have a

mean of 50 and a SD of 10. All scores obtained <50 can be interpreted as below the US or Japanese general population T-score; scores >50 can be interpreted as above the US or Japanese general population score

Figure 13: Conceptual framework for the SF-36 v2 questionnaire



Sample size

UX023T-CL201

Fifteen subjects were planned to be enrolled in the study. This sample size would provide a 95% confidence interval (CI) with the half width no greater than 24.8%, assuming the proportion of subjects with a phosphorus level above the LLN at 2 weeks after dosing, as averaged across dose cycles between baseline and Week 24 was 60%. A reduction in excess osteoid was expected to be shown in all subjects with paired biopsies, with an estimated ≥ 50% reduction from Baseline in osteoid thickness. The sample size and study duration were believed to be sufficient to enable characterization of burosumab effects on serum phosphorus levels, excess osteoid histomorphometric indices, and the safety profile of burosumab.

KRN23-002

A national questionnaire survey by the Hormone Receptor Abnormality Research Committee has shown that the number of patients diagnosed as having TIO in Japan was 35.

When the number of TIO patients aged 18 years or older, the study subjects for this study, was investigated at 8 sites in Japan, the total number of TIO patients was calculated at 28, and 15 of such patients were estimated to be subjects for this study. In consideration of the feasibility of the study (e.g., frequency of study visits), the number of enrollable subjects was judged to be about 4. Also in Korea, a similar investigation was conducted at 3 sites and the number of patients as the subjects for this study

was estimated to be 10 and, in consideration of the feasibility of the study, the number of enrollable subjects was judged to be about 2. Based on these considerations, the number of subjects enrollable in the present study was judged to be about 6.

Randomisation

Not applicable. Both studies were single-arm studies in which all subjects received investigational product.

UX023T-CL201

Subjects were to be selected for screening only if they were deemed to be inoperable for cure. A historical tumour image could be used as the screening image if it was obtained within 12 months of screening. Due to that this was the first study of KRN23 in subjects with TIO or ENS-associated osteomalacia, subjects were to be enrolled sequentially; to minimize any safety risks the first 3 subjects must complete at least the first 2 doses with no safety or tolerability issues before the next 12 subjects could be enrolled.

KRN23-002

The Investigators performed screening after obtaining informed consent in writing from subjects. The subjects who were ascertained to be eligible were enrolled into the study within 21 days after the screening. After enrolment, a baseline examination was conducted. KRN23 treatment was initiated 1 to 3 days after the baseline examination, and within 35 days after the enrolment for the subjects who underwent bone biopsy or within 21 days after the enrolment for the subjects who did not undergo bone biopsy.

Blinding (masking)

Not applicable. Both studies were open label.

Study KRN23-002

The applicant considered that no observer bias could occur in the evaluation of serum phosphorous, which was the measurement for the primary endpoint. For the assessment of 99mTc bone scan, standard X-ray examination, renal ultrasound, TIO/ENS imaging, and bone biopsy, the person in charge of assessment was furnished solely with the relevant data, i.e., no other information concerning the relevant subject was provided.

Statistical methods

UX023T-CL201

The submitted study UX023T-CL201 CSR summarizes efficacy and safety analyses through Week 144 for subjects with TIO (N = 14) and includes all planned analyses for all enrolled subjects (N = 17).

Analyses of the data were to be performed when the first 3 subjects had completed their Week 12 visit. An additional analysis was to occur using all available data when the first subject had completed the post-treatment bone biopsy and could occur at other time points.

The protocol-defined statistical analyses were detailed in the statistical analysis plan (version 1.0, dated 04 May 2016) before the analyses for this report were conducted. The Statistical Analysis Plan, Version 1.0, has been submitted.

Statistical analyses have been reported using summary tables, figures, and data listings. Where applicable statistical tests were 2-sided at an alpha = 0.05 significance level and 2-sided 95% confidence intervals (CIs) have been presented. All p-values are presented as nominal p-values. There was no adjustment made for multiplicity.

Analysis sets

Full Analysis Set: All efficacy (except bone biopsy endpoints), safety, and PK/PD analyses will be performed on the set of all subjects who received at least 1 dose of investigational product.

Biopsy Analysis Set: The biopsy analysis set will include enrolled subjects with Baseline and follow-up (either Week 48 or ET prior to Week 48) bone biopsy data.

Primary Efficacy Analysis

The proportion of subjects who achieved a serum phosphorus level above the LLN (2.5 mg/dL [0.81 mmol/L]), at 2 weeks after dosing (between baseline and Week 24, on average) was provided, along with the 2-sided 95% confidence interval using the Wilson score method. Additional analyses of serum phosphorus including observed values, change from Baseline, percent change from Baseline over time, and area under the curve were summarized from Baseline to Week 24.

For Histomorphometric indices O.Th, OS/BS, OV/BV and MLt at baseline, Week 48, both change from baseline, and percent change from baseline at Week 48 were summarized. Change from baseline at Week 48 will be tested using a t-test if the normality assumption is valid. If the normal assumption is invalid, a sign test will be used.

Handling of Missing and Incomplete Data

For all analyses, missing data was treated as missing, unless otherwise specified. When a change from baseline was assessed, only subjects with a baseline and at least one post-baseline measurement was included in the analysis

Missing Data in Bone Biopsy Parameter MLt

If the MLt data was missing due to low quality of the bone biopsy sample (i.e. no bone biopsy parameters are available for that sample), the MLt parameter was to be set to missing for the sample. If the MLt data was missing due to very little label uptake because of the mineralization defect (i.e. there is at least one bone biopsy parameter available for that sample), the MLt was to be imputed as O.Th/(MAR*MS/OS), where MAR was imputed as 0.3 µm/day, with O.Th, MS and OS from the same visit of the same subject (Dempster et al. 2013). If any of O.Th, MS or OS at that visit for the subject was missing, MLt was to be set as missing.

Secondary endpoints

Summaries have been provided.

Interim Analyses

Administrative analyses were performed to support regulatory activities or product development per the Sponsor’s decision. The primary analysis was conducted when subjects completed the Week 48 assessments.

Data Monitoring Committee

Based on the open-label study design, safety will be monitored by Ultragenyx. An independent data monitoring committee will not be used.

KRN23-002

In the CSR it is stated that no changes were made to the planned statistical analysis provided in the protocol. No amendments were made to the SAP and PAP, which were finalized prior to interim database lock. The SAP provided is version 1.0 dated 12 April 2018. The statistical analysis plan was created based on the protocol version J2.0.M. The SAP identified a single instance of a change in the planned analysis: "The achievement number and proportion of mean phosphorus in secondary endpoints will be calculated except in the case that the data obtained at all evaluation time points are missing".

No changes following interim database lock were made. As post-hoc analyses, other adverse events of special interest were analysed.

Analysis sets

The "efficacy analysis set" included all eligible subjects who had received at least one dose of KRN23 and had serum phosphorus concentration data after KRN23 treatment initiation.

The "safety analysis set" included all eligible subjects who had received at least one dose of KRN23.

The "pharmacokinetic analysis set" included all eligible subjects who had received at least one dose of KRN23 and in whom blood had been collected for serum KRN23 concentration measurement after KRN23 treatment initiation.

Primary Endpoint

Descriptive statistics of serum phosphorus concentration at each test time point were calculated and a summary of serum phosphorus concentration over time have been presented in a table. In addition, mean serum phosphorus concentration values over time have been plotted in a graph with the week on the X axis, and the mean values on the Y axis.

Secondary Endpoints

Descriptive statistics of changes and percentages change from baseline of the following histomorphological parameters, as measured at Week 48, were to be calculated including osteoid Thickness (O.Th), osteoid surface/Bone surface (OS/BS), osteoid volume/Bone volume (OV/BV) and mineralization lag time (MLt)

Descriptive statistics of the changes from baseline of serum levels of FGF23, ALP, and 1,25(OH)2D and urinary levels of phosphorus, TRP, and TmP/GFR were to be calculated. In addition, mean values and mean changes from baseline were to be plotted with the week on the X axis, and the mean values and mean change from baseline on the Y axis.

Descriptive statistics of the changes and percent changes from baseline of serum bone biomarkers (CTx, P1NP, BALP, and OC) were to be calculated.

Multiple Comparison/Multiplicity

Multiplicity was not considered.

Interim Analyses and Data Monitoring

Data cut-off will be performed at the time all the subjects (excluding those who withdrew from KRN23 treatment) have completed the examination at Week 24, and at the time after completion of Week 48 examination.

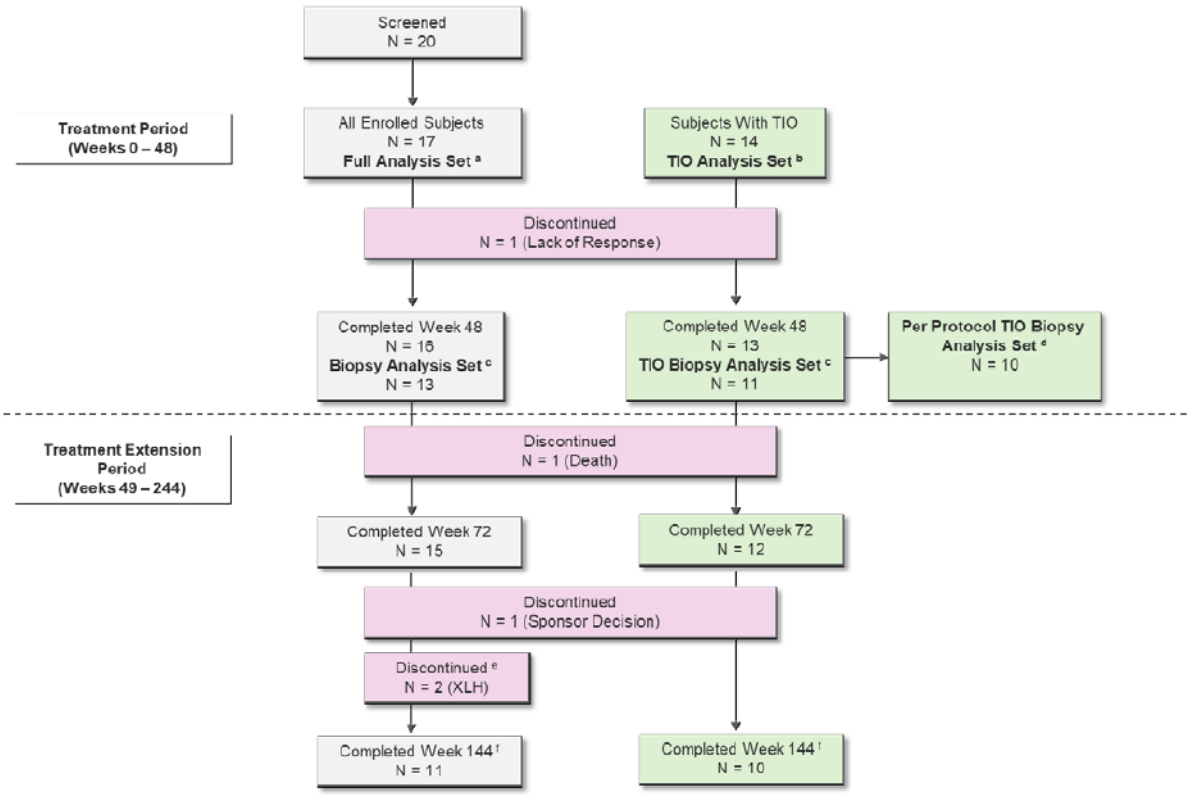
Results

Participant flow

UX023T-CL201

Seventeen subjects enrolled in the study, of which 14 subjects had TIO and 1 subject had ENS-associated osteomalacia. Two subjects who were enrolled in the study with a clinical diagnosis of TIO were later found to have XLH based on genetic testing. A total of ten TIO-subjects have reached Week 144 at the data lock point for this report (Figure 14).

Figure 14: Subject Disposition (All Enrolled Subjects) (UX023T-CL201)



[a] All enrolled subjects who received at least 1 dose of burosumab.
[b] Excludes 2 subjects with XLH and I subject with ENS-associated osteomalacia.
[c] All enrolled subjects in the corresponding analysis set with baseline and Week 48 bone biopsy data.
[d] Excludes 1 subject who received minimal burosumab dosing on study.
[e] Two subjects were found to be positive for PHEX mutations during the study, and were therefore discontinued prior to Week 144.
[f] One subject had not completed the Week 144 visit as of the data cutoff date (11 Jan 2019).

The following five subjects discontinued the study as of the data cut-off date:

- *One subject (TIO)* died due to a serious TEAE (considered not related to burosumab by the Investigator).
- *One subject (TIO)* discontinued burosumab treatment due to serious TEAE, and was subsequently discontinued from the study due to lack of phosphorus increase in response to burosumab (the highest burosumab dose that the subject had received during the study was 1.4 mg/kg).
- *One subject (TIO)* was discontinued from the study per the Sponsor's decision, that was also supported by the Investigator, as the subject's serum phosphorus levels were mostly in the normal range throughout the study and therefore, the subject received minimal burosumab dosing during the study (a total of 4 doses up to Week 72, ranging from 0.15 to 0.3 mg/kg).

- *One subject (XLH)* was discontinued from the study as this subject was found to no longer met the eligibility criteria for the study.
- *One subject (XLH)* was discontinued from the study as this subject was found to no longer met the eligibility criteria for the study.

KRN23-002

The subject disposition is summarised in Table 14.

Table 14: Subject Disposition (KRN23-002)

	Total N = 14	
	n	(%)
Consented	14	
Consented (Bone Biopsy)	4	
Ineligible/dropout	0	
Enrolled	14	
Removed before the first dose of investigational product	1	(7.1)
Received investigational product	13	(92.9)
Discontinued after the first dose of investigational product	1	(7.1)
Reason for discontinuation including before the first dose of investigational product		
Withdrawal by Subject	1	
Adverse Event or Disease Progression	1	
Discontinuation by period		
Week 0 - Week 11		
Week 12 - Week 23	1	
Week 24 - Week 35		
Week 36 -		
Completed	12	(85.7)

N: Number of subjects enrolled.
Percentages are based on the number of subjects enrolled.

The following subjects discontinued the study as of the data cut-off date:

- One subject received four doses of burosumab treatment over 12 weeks before discontinuing from the study. The dose was titrated up to 1.0 mg/kg at Week 12. There were no post-dose key efficacy response data or tumour data as the subjects only received four doses.
- One subject was removed before the start of KRN23 administration because of withdrawal by subject

As of the cut-off date, 4 subjects had self-administered KRN23 in hospital. Two subjects had self-administered KRN23 at home.

Recruitment

UX023T-CL201

The study was conducted at eight centres in the United States.

The Study Start Date was 24 March 2015 (date of first signed informed consent).

KRN23-002

This study was conducted at four sites in Japan and three sites in South Korea

The Study Start Date was 2 May 2016 (date of consent of the first subject)

Conduct of the study

UX023T-CL201

Changes to the Conduct of the Study

The original protocol was dated 29 August 2014. There were five protocol amendments.

Amendment 1 was dated 21 January 2015, i.e. before the start of the study.

Amendment 2 was dated 14 October 2015. This amendment included an increase of sample size from approximately 6 to approximately 15 adult subjects. Also, sections of the protocol was updated to specify the co-primary efficacy evaluations (i.e., change from baseline in serum phosphorus levels over time and percent change from baseline in osteomalacia parameters at 48 weeks as determined by histomorphometric evaluation of trans-iliac crest bone biopsies).

Amendment 3 was dated 17 February 2016. This amendment included an extension of the study duration: After completion of the 48-week treatment period, subjects could continue treatment for up to an additional 96 weeks in the Treatment Extension Period.

Amendment 4 was dated 10 November 2017. Treatment duration was extended to 216 weeks or until 30 June 2019. The maximum volume of a burosumab injection was increased from 1.0 to 1.5 mL. The wording of the co-primary endpoint regarding histomorphometry assessments was updated from percent change from baseline to change from baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of KRN23 treatment using the following histomorphometric indices: O.Th, OS/BS, OV/BV, and MLt.

Amendment 5 (dated 27 April 2018) was implemented at the clinical sites after 10 January 2018, the data cut-off date for the application of this variation. The amendments included introducing a mutational analysis of the PHEX gene to rule out a possible XLH diagnosis due to the similar clinical features of the diseases in specific subjects who had clinical symptoms and hypophosphatemia since childhood and in whom the tumour had not been identified.

Protocol deviations

During the study, a total of 5 subjects (35.7%) in the TIO Analysis Set had at least one major protocol deviation (n=8).

Four subjects had a major deviation regarding the timing of signing an updated ICF. One subject had a major protocol deviation under the category of "Procedure Not Done", that included not having a urine pregnancy test performed at Screening and subsequent visits because of uncertainty about the subject's menopausal status. Three subjects had a major protocol deviation under the category "other".

As discussed above, two subjects were tested and found to be positive for PHEX mutations and were diagnosed with XLH. These 2 subjects were also considered to have major protocol deviations in the category "other" and excluded from the TIO Analysis Set.

KRN23-002

Protocol amendments Japan

The original protocol was dated 30 November 2015.

Selected protocol amendments are shown in Table 15

Table 15: Summary of Protocol Amendments (Japan) (excerpt)

Version	Date of Initial Release / Amendment	Major Amendment
J1.0.M	30 November, 2015	Initial version
J1.2.M	8 March, 2016	• A description of exclusion criterion 4) was changed to adequately exclude inappropriate patients to participate in this study • ^{99m}Tc bone scan, DXA, and radiographs were added as exploratory endpoints. • The basal point of study-visit allowance was clarified. • The dosing schedule of TC was changed to be the same as that in the overseas trial. • Measurement of amylase isozyme was added. • Procedures for echocardiography and DXA were changed to follow procedures at each investigative site.
J1.3.M	6 June, 2016	• The target number of subjects was changed in consideration of the feasibility of the study • The allowance period for examination was modified. • The sampling timing of serum Cr used for calculation of TmP/GFR was clarified.
J1.5.M	10 November, 2016	• Dose adjustment criteria were modified. • The description was changed to clarify that bone biopsy at Week 48 or ET was not to be performed when no bone biopsy sample was obtained at baseline.
J2.0.M	14 March, 2017	• Dosing duration was extended from 48 weeks to 144 weeks. • Week 48 examinations were included to the cut-off • Self-administration was allowed if the subjects were considered to be able to inject by themselves.

Protocol amendments Korea

The original protocol was dated 19 January 2016.

Selected protocol amendments are shown in Table 16.

Table 16: Summary of Protocol Amendments (Korea) (excerpt)

Version	Date of Initial Release / Amendment	Major Amendment
K1.1	19 January, 2016	Initial version for Korea based on the version J1.1.M
K1.2	14 March, 2016	• A description of exclusion criterion 4) was changed to adequately exclude inappropriate patients to participate in this study • ^{99m}Tc bone scan, DXA, and radiographs were added as exploratory endpoints. • The basal point of study-visit allowance was clarified. • The dosing schedule of TC was changed to be the same as that in the overseas trial. • Measurement of amylase isozyme was added. • Procedures for echocardiography and DXA were changed to follow procedures at each investigative site.
K1.3	24 June, 2016	• The target number of subjects was changed in consideration of the feasibility of the study. • The allowance period for examination was modified. • The sampling timing of serum Cr used for calculation of TmP/GFR was clarified.
K1.5	16 November, 2016	• Dose adjustment criteria were modified. • The description was changed to clarify that bone biopsy at Week 48 or ET was not to be performed when no bone biopsy sample was obtained at baseline.
K2.0	17 March, 2017	• Dosing duration was extended from 48 weeks to 144 weeks. • Week 48 examinations were included to the cut-off data

Baseline data

Demography

The baseline demography for the TIO Analysis Set of study UX023T-CL201 and the Efficacy Analysis Set of KRN23-002 is summarised in Table 17.

Table 17: Subject Demographics for Study UX023T-CL201 (TIO Analysis Set) and Study KRN23-002 (Efficacy Analysis Set)

Parameter Statistics	UX023T-CL201 (N = 14)	KRN23-002 (N = 13)
Age (years)		
Mean (SD)	56.9 (10.25)	60.5 (10.8)
Median (min, max)	59.5 (33, 68)	58.0 (41, 73)
Age Group - n (%)		
18 to 65 years	10 (71%)	8 (62%)
> 65 years	4 (29%)	5 (38%)
Sex - n (%)		
Male	8 (57%)	6 (46%)
Female	6 (43%)	7 (54%)
Country - n (%)		
United States	14 (100%)	-
Japan	-	9 (69%)
Korea	-	4 (31%)
Weight (kg)		
Mean (SD)	94.2 (20.29)	61.4 (13.02)
Median (min, max)	92.2 (65.8, 150)	62.5 (36.4, 82.2)

SD = standard deviation.

Baseline biochemical parameters

The baseline disease laboratory characteristics for both studies are summarised in Table 18.

Table 18: Baseline Biochemical Disease Characteristics for Study UX023T-CL201 (TIO Analysis Set) and Study KRN23-002 (Efficacy Analysis Set)

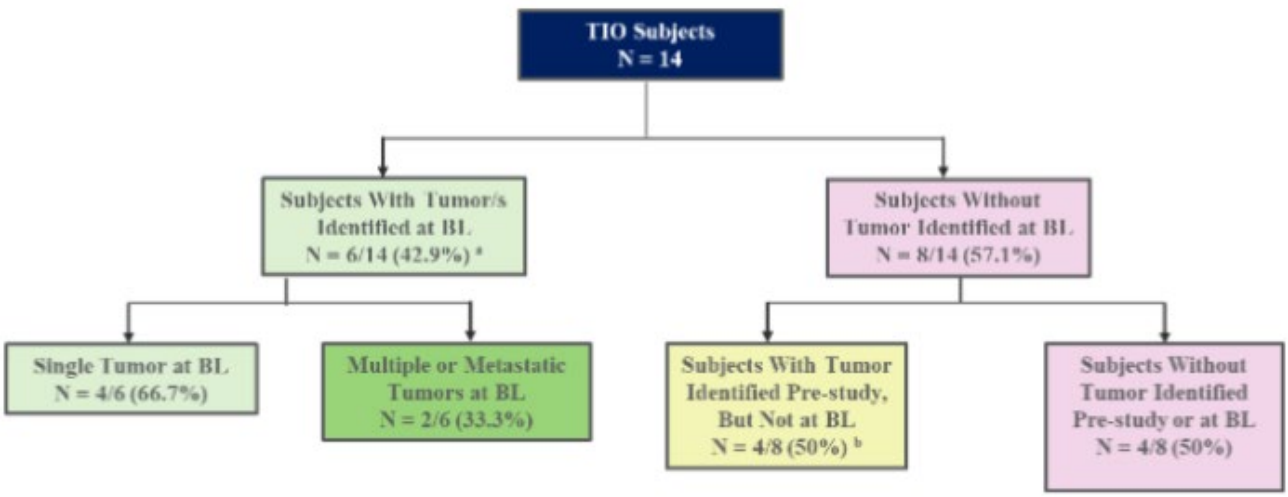
Parameter Statistics	UX023T-CL201 (N = 14)	KRN23-002 (N = 13)
Serum Total FGF23 (pg/mL)		
Mean (SD)	770 (797.7)	1019 (1668.8)
Median (min, max)	416 (93.9, 2569)	320 (106, 5150)
Serum Phosphate (mg/dL)		
Mean (SD)	1.60 (0.474)	1.62 (0.49)
Median (min, max)	1.55 (1.0, 2.9)	1.60 (0.9, 2.7)
TmP/GFR (mg/dL)		
Mean (SD)	1.12 (0.539)	1.15 (0.43)
Median (min, max)	0.94 (0.6, 2.7)	1.07 (0.5, 2.2)
$1,25(OH)_2D$ (pg/mL)		
Mean (SD)	26.0 (8.78)	22.6 (11.9)
Median (min, max)	23.3 (14.5, 42.7)	18.2 (9.6, 50.1)

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; FGF23 = fibroblast growth factor 23; SD = standard deviation; TIO = tumour-induced osteomalacia; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate.

Tumour disposition

In Study UX023T-CL201, the tumour location and type had been determined prior to the study for 10 of the 14 subjects with TIO (71.4%) in Study UX023T-CL201 (Figure 15). For one of these 10 subjects, the underlying tumour was identified for the first time at Screening. Tumours had never been located in 4/14 subjects (28.6%), and TIO was diagnosed based on clinical symptoms and biochemical evidence.

Figure 15: Tumour Disposition at Study Baseline (UX023T-CL201)



[a] 5/6 subjects with tumor detected at baseline underwent one or more surgeries to remove tumor prior to study entry. One subject (156-103) had their tumor imaged and identified for the first time at Screening, and therefore did not undergo prior surgical resection of the tumor.
[b] 4/4 subjects with tumor identified previously, but not at study baseline, underwent surgery to remove tumor. Tumor was not located at study baseline in these subjects with previously identified tumors possibly due to small size, location of tumor, or imaging technique used.

In Study KRN023-002, the tumour location and type had been identified prior to the study for nine of 13 subjects (69%). Tumours had never been located in 4/13 subjects (31%), and TIO had been diagnosed based on clinical symptoms and biochemical evidence.

TIO Treatment History

The characteristics of the TIO treatment history in both studies are summarised in Table 19.

Table 19: TIO Disease History and Management Before Enrolment in Study UX023T-CL201 (TIO Analysis Set) and in Study KRN23-002 (Efficacy Analysis Set)

Parameter **Statistics**	**UX023T-CL201** **(N = 14)**	**KRN23-002** **(N = 13)**
Time Since First Symptoms (years)		
Mean (SD)	18.0 (12.6)	10 (5)[a]
Median (Min, Max)	16.7 (2.6, 37.8)	11.3 (1.7,17.5)
Time Since Diagnosis (years)		
Mean (SD)	13.7 (12.95)	6.8 (3.8)
Median	8.8 (0.7, 35.8)	7.9 (0.9,11.8)
Prior Surgery to Remove Tumour		
n (%)	9 (64.3%)	7 (53.8%)
Treatment With Oral Phosphate		
n (%)	13 (92.9%)	12 (92.3%)
Duration, Mean (SD), years	10.5 (12.18)	N/A
Treatment With Active Vitamin D		
n (%)	14 (100%)	13 (100%)
Duration, Mean (SD), years	10.4 (12.46)	N/A

SD = standard deviation; TIO = tumour-induced osteomalacia.
a: n=12.

Dosing

Burosumab dosing is given in Table 20

Table 20: Categorical and Mean Burosumab Dose Summary in Studies UX023T-CL201 (TIO Analysis Set) and KRN23-002 (Efficacy Analysis Set)

	Dose by Category			Mean (SD) Dose (mg/kg)	
Visit	Dose Category (mg/kg)	UX023T-CL201 (N = 14) n (%)	KRN23-002 (N = 13) n (%)	UX023T-CL201 (N = 14)	KRN23-002 (N = 13)
Baseline	0.3	14 (100)	13 (100%)	0.3 (0.00)	0.3 (0.00)
Week 16	≤ 0.3	3 (21.4)	3 (23.1)	0.79 (0.362)	0.66 (0.35)
	0.4 – 0.9	5 (35.7)	6 (46.2)		
	1.0 – 1.5	5 (35.7)	3 (23.1)		
	1.6 – 2.0	-	-		
Week 24	≤ 0.3	3 (21.4)	3 (23.1)	0.8 (0.42)	0.74 (0.45)
	0.4 – 0.9	4 (28.6)	4 (30.8)		
	1.0 – 1.5	4 (28.6)	4 (30.8)		
	1.6 – 2.0	1 (7.1)	1 (7.7)		
Week 48	≤ 0.3	3 (21.4)	3 (23.1)	0.87 (0.487)	0.91 (0.59)
	0.4 – 0.9	4 (28.6)	4 (30.8)		
	1.0 – 1.5	4 (28.6)	3 (23.1)		
	1.6 – 2.0	1 (7.1)	2 (15.4)		
Week 72/88 [a]	≤ 0.3	4 (28.6)	3 (23.1)	0.73 (0.535)	0.96 (0.70)
	0.4 – 0.9	4 (28.6)	1 (7.7)		
	1.0 – 1.5	2 (14.3)	4 (30.8)		
	1.6 – 2.0	1 (7.1)	3 (23.1)		
Week 144 [b]	≤ 0.3	4 (28.6)	-	0.71 (0.556)	-
	0.4 – 0.9	3 (21.4)	-		
	1.0 – 1.5	1 (7.1)	-		
	1.6 – 2.0	1 (7.1)	-		

a: Week 72 for Study UX023T-CL201 and Week 88 for Study KRN23-002. One subject was not dosed at Week 88 in Study KRN23-002.

b: One subject had not completed the Week 144 visit as of the data cut-off date, and one subject was not dosed at Week 144.

The decrease in the median dose at Weeks 96 and 144 can be explained by the discontinuation of one subject who was receiving doses > 1 mg/kg, dose reduction in one subject following an event of hyperphosphatemia, and dose reduction in one subject following tumour resection.

Outcomes and estimation

Results are summarised up to Week 144 for Study UX023T-CL201 and up to Week 88 for Study KRN23-002.

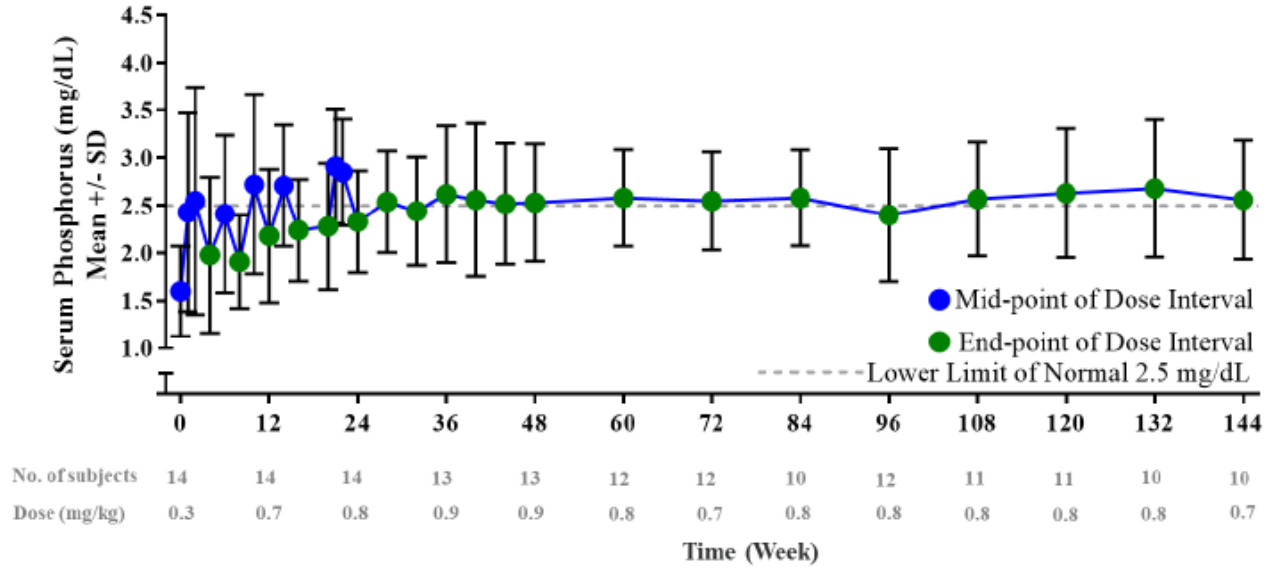
PD endpoints across TIO studies

The proportion of subjects achieving mean serum phosphorus levels > 2.5 mg/dl at the mid-point of the dosing cycle was a Co-primary endpoint in Study UX023T-CL201 and Serum phosphate concentration at each test time point was the primary endpoint in Study KRN23-002.

Serum phosphate levels are shown in Figure 16 and a summary of PD endpoints is given in Table 21.

Figure 16: Serum Phosphate Levels (Mean ± SD) (mg/dL) Over Time in Studies UX023T-CL201 and KRN23-002

A) Study UX023T-CL201 (TIO Analysis Set)



B) Study KRN23-002

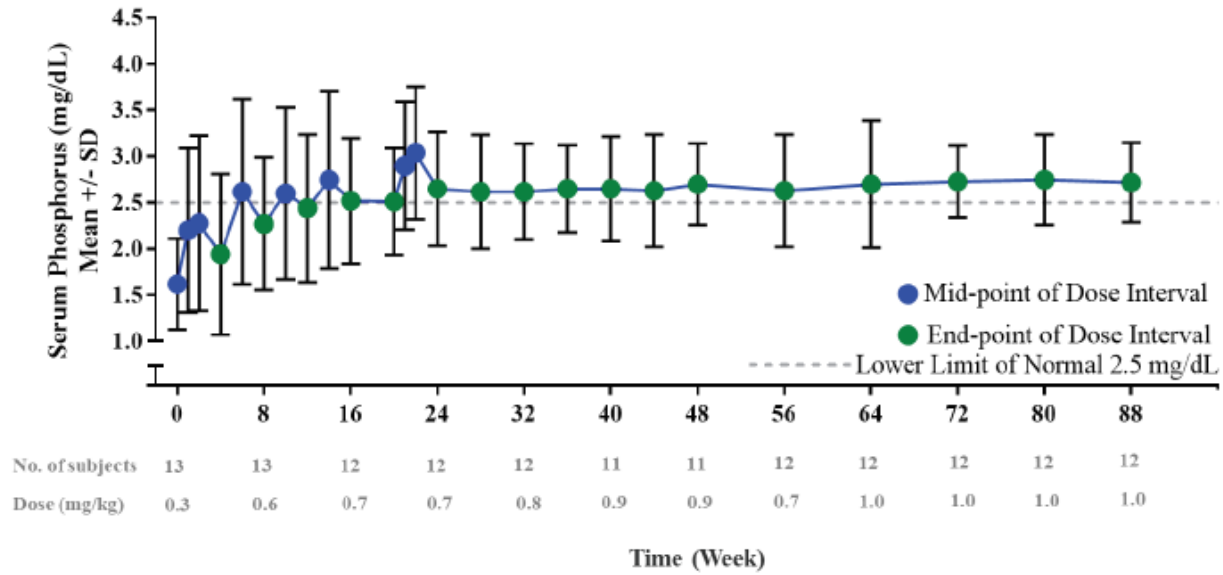


Table 21: Summary of PD Endpoints in Studies UX023T-CL201 and KRN23-002

Parameter Statistic	Study UX023T-CL201 N = 14	Study KRN23-002 N = 13
Serum Phosphate		
Baseline, mean (SD), mg/dL	1.60 (0.474)	1.62 (0.49)
Week 144/88 [a], mean (SD), mg/dL	2.56 (0.624)	2.72 (0.43)
Mean across the midpoint of the dose intervals to Week 24 (mg/dL) - mean (SD)	2.64 (0.76)	2.63 (0.87)
Proportion of subjects achieving a mean serum phosphate level above LLN (2.5 mg/dL) at midpoints of dose interval between Baseline and Week 24 - n (%) [b]	7 (50.0)	9 (69.2)
Proportion of subjects achieving a serum phosphate level above LLN (2.5 mg/dL) after titration at Week 22 - n (%)	11 (78.6)	10 (76.9)
TmP/GFR (mg/dL)		
Baseline, mean (SD)	1.12 (0.54)	1.15 (0.43)
Week 144/72 [a], mean (SD)	2.18 (0.669)	2.29 (0.496)
Serum $1,25(OH)_2D$ (pg/mL)		
Baseline, mean (SD)	25.9 (8.78)	22.6 (11.9)
Week 144/72 [a], mean (SD)	32.0 (12.49)	41.3 (8.53)

$1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; LLN = lower limit of normal; SD = standard deviation; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate.

a: Last available time points presented (Week 144 for Study UX023T-CL201 and Week 88 or Week 72, as applicable, for Study KRN23-002).

b: Co-primary endpoint in Study UX023T-CL201.

A total of seven (50%) subjects (95% CI: 26.8, 73.2) in the TIO Analysis Set achieved a mean serum phosphate level above the LLN as averaged across the midpoint of the dose intervals (i.e., 2 weeks after dosing) between baseline and Week 24 (Co-primary endpoint).

In Study UX023T-CL201, two subjects did not have increases in serum phosphate to above the LLN with burosumab treatment. Both subjects had very high FGF23 levels at baseline:

One subject discontinued burosumab treatment due to a serious TEAE at Week 24. The subject was subsequently discontinued from the study at Week 36 due to lack of phosphate increase in response to burosumab (the highest burosumab dose that the subject had received during the study was 1.4 mg/kg) and due to the Investigator's referral to chemotherapy treatment.

One subject experienced two serious TEAEs on study that were considered unrelated to burosumab treatment and were consistent with the subject's medical history of continued progression of the underlying tumour; doses were increased to a maximum of 2 mg/kg Q2W. No serum phosphate data are available after the Week 144 dose; no hyperphosphataemia or other safety findings potentially related to burosumab were noted with the Q2W dosing.

In Study KRN23-002, three subjects failed either to achieve serum phosphorous levels above LLN or to maintain an increase in terms of and expectation of burosumab efficacy in a TIO patient population:

- One subject: serum phosphorous remained below LLN through to Week 88
- One subject: serum phosphorous remained below LLN until early termination at Week 14
- One subject: serum phosphorous achieved normal levels on only 2 occasions through to Week 88

Histomorphometric Indices of Osteomalacia

The change from Baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of KRN23 treatment using histomorphometric indices OV/BV, OS/BS, O.TH and Mlt was a co-primary endpoint in Study UX023T-CL201.

Of the 14 subjects with TIO in Study UX023T-CL201, 11 subjects had paired bone biopsies at Baseline and Week 48 and comprised the TIO Biopsy Analysis Set.
Most subjects in the TIO Biopsy Analysis set (9/11; 82%) presented with osteomalacia (qualitatively graded as mild [three subjects] and severe [six subjects]) as demonstrated by an excess of osteoid tissue (assessed by osteoid volume, surface, and thickness) and delay in Mlt (time from osteoid deposition to mineralisation). Two subjects (18%) did not have osteomalacia at baseline based on the qualitative assessment, although Mlt was prolonged in these subjects, and bone formation activity was low as evidenced by minimal or absent tetracycline label.

All subjects had previously been treated with oral phosphate/active vitamin D, and most subjects with severe osteomalacia (five of six [83%]) had received SoC treatment for >5 years.
In eight subjects in the TIO Analysis Set, in whom Mlt was not measurable, Mlt was calculated using an established imputation technique (Dempster et al. 2013).

The histomorphometric data from Study UX023T-CL201 are summarised in Table 22

Table 22: Histomorphometry Results and Reference Ranges – Study UX023T-CL201 (TIO Analysis Set)

Parameter Statistic	TIO Biopsy Analysis Set (N = 11) Baseline	TIO Biopsy Analysis Set (N = 11) Week 48	Reference Ranges (Glorieux et al. 2000) (N = 12)[a]	Reference Ranges (Recker et al. 1988) (N = 30 – 34)[b]
Osteoid Volume/Bone Volume (OV/BV [%])			-	-
Mean (SD)	17.6 (19.5)	12.1 (15.4)	1.57 (0.67)	1.85 (1.07)
Min, Max	1.3, 63.4	1.8, 50.2	0.41, 3.05	0.30, 3.10
Change From Baseline, Mean (95% CI)	-5.5 (-11.9, +0.9)			
p value	0.0858			
Osteoid Thickness (O.Th [µm])				
Mean (SD)	16.5 (12.0)	11.3 (9.2)	6.9 (1.2)	9.27 (2.10)
Min, Max	3.5, 41.3	5.1, 35.4	5.4, 8.9	5.50, 12.00
Change From Baseline, Mean (95% CI)	-5.1 (-10.0, -0.2)			
p value	0.0428			
Osteoid Surface/Bone Surface (OS/BS [%])				
Mean (SD)	56.8 (31.0)	56.6 (26.3)	16.5 (5.4)	14.3 (6.3)
Min, Max	15.0, 98.0	23.0, 96.0	4.9, 23.9	7.0, 25.0
Change From Baseline, Mean (95% CI)	-0.2 (-13.9, +13.5)			
p value	0.9770			
Mineralisation Lag Time (Mlt [days]) (includes imputed values[c])				
Mean (SD)	1598 (1327)	940 (2157)	17.3 (6.5)	50.2 (41.9)
Min, Max	277, 4267	18, 7375	9.3, 28.6	15.0, 50.0
Change From Baseline, Mean (95% CI)	-565 (-2037, +907)			
p value	0.4077			

TIO = tumour-induced osteomalacia.
a: Healthy, young men (n=5) and women (n=7), age 17-23 years.
b: Healthy, postmenopausal women, age 45-74 years.
c: Mlt was evaluable at both baseline and Week 48 for three subjects, imputed at baseline and evaluable at Week 48 for six subjects, and imputed at both baseline and Week 48 for two subjects. Histomorphometric parameters used for Mlt imputation are summarised for individual subjects in UX023T-CL201 Week 144 CSR, Table 13.

Two subjects were qualitatively evaluated as having no osteomalacia at baseline based on normal osteoid volume, despite having prolonged Mlt. In both subjects, bone formation activity was extremely low, as demonstrated by the absence of/minimal tetracycline double label. After 48 weeks of burosumab treatment, bone formation improved in both subjects, as shown by an increase in mineralisation surface, indicating improved mineralisation and improved bone formation. While the osteoid volume per bone volume increased in both subjects, this change is likely due to increased bone turnover at Week 48

compared with baseline, and the fact that mineralisation had improved on burosumab but had not yet completely normalised.

Comparisons were made between the TIO Biopsy Analysis Set of Study UX023T-CL201 and the adult XLH bone biopsy study UX023-CL304.

Table 23: Osteomalacia Parameters at Baseline and Week 48 in TIO UX023T-CL201 and XLH UX023-CL304 Studies

Parameter Statistic	TIO Biopsy Analysis Set (N = 11)	TIO Biopsy Analysis Set, Severe OM Subgroup (N = 6)	XLH UX023-CL304 (N = 11)
Osteoid Volume/Bone Volume (%)			
Baseline, mean (SD)	17.6 (19.49)	28.7 (20.77)	26.1 (12.36)
Week 48, mean (SD)	12.1 (15.44)	18.1 (19.42)	11.9 (6.6)
Percent Change from Baseline [a]	31.3	36.9	54.4
Osteoid Surface/Bone Surface (%)			
Baseline, mean (SD)	56.8 (31.0)	75.2 (27.07)	91.7 (3.44)
Week 48, mean (SD)	56.6 (26.35)	64.2 (29.84)	67.8 (13.67)
Percent Change from Baseline [a]	0.004	14.6	26.1
Osteoid Thickness (µm)			
Baseline, mean (SD)	16.5 (12.04)	22.6 (12.71)	17.2 (4.11)
Week 48, mean (SD)	11.3 (9.19)	14.6 (11.77)	11.6 (3.11)
Percent Change from Baseline [a]	31.5	35.4	32.6
Mineralisation Lag Time (days) [b]			
Baseline, mean (SE)	667 (414)	-	594 (675)
Week 48, mean (SE)	331 (396)	-	156 (77)
Percent Change from Baseline [a]	50.4	-	74
Mineralisation Lag Time Evaluability, n (%)			
Baseline Evaluable-> Week 48 Evaluable	3 (27.3)	0	6 (54.5)
Baseline Not Evaluable-> Week 48 Not Evaluable	2 (18.2)	2 (33.3)	1 (9.1)
Baseline Not Evaluable-> Week 48 Evaluable	6 (54.5)	4 (66.7)	4 (36.4)

Mlt = mineralisation lag time; OM = osteomalacia; SE = standard error; SD = standard deviation; TIO = tumour-induced osteomalacia.

a: Represents the percent change in the mean Week 48 value compared to the mean baseline value.

b: Mlt results are provided for subjects with measurable Mlt at baseline (n = 3 for Study UX023T-CL201 and n = 6 for Study UX023-CL304).

In Study KRN23-002, bone biopsies were an optional procedure, and therefore limited data are available on osteomalacia at baseline in this study population. Three subjects underwent bone biopsies at baseline, and all three subjects had severe osteomalacia, despite treatment with long-term therapy with oral phosphate/active vitamin D (Table 24).

Table 24: Histomorphometry Results – Study KRN23-002

	Subject 101-02		Subject 101-03		Subject 102-03	
Parameter	**Baseline**	**Week 48**	**Baseline**	**Week 48**	**Baseline**	**Week 48**
OV/BV	7.1%	8.6%	3.5%	4.1%	31.5%	15%
O.Th	8.7 µm	13.6 µm	7.6 µm	6.4 µm	31.8 µm	20.5 µm
OS/BS	38%	37%	31%	44%	74%	48%
Mlt	-[a]	-[a]	-[a]	49.1 days	-[a]	738.7 days
Osteomalacia assessment	Severe	Severe	Severe	Mild	Severe	Mild

Mlt = mineralisation lag time; OS/BS = osteoid surface/bone surface; O.Th = osteoid thickness; OV/BV = osteoid volume/bone volume.
a: Could not be determined because tetracycline labels were too blurred.

Bone Fractures and Pseudofractures

In Study UX023T-CL201 total of 249 nontraumatic active fractures and pseudofractures were detected on 99mTC- labelled whole body bone scan conducted at baseline, indicative of the underlying osteomalacia and poor bone quality at study entry. Bone scans on treatment were compared to baseline scans by a central reader who was blinded to subject data

The number of new fractures/pseudofractures detected via bone scan decreased over time, from 19 and 17 new active fractures/pseudofractures identified at Weeks 24 and 48, respectively, to three new active fractures each and no new pseudofractures identified at Weeks 96 and 144 (Table 25). Of note, all three new active fractures identified at Week 144 were in one subject who did not show an optimal response with burosumab treatment, possibly due to a very high tumour burden and FGF23 levels.

Table 25: Active Fractures and Pseudofractures Over Time as Assessed by 99mTc Bone Scans in Study UX023T-CL201 (TIO Analysis Set)

Parameter Statistic	Week 24 N = 14	Week 48 N = 13[a]	Week 96 N = 12[b]	Week 144 N = 10[c]
Total Fractures/Pseudofractures at Baseline = 249				
Healed, n (% of Baseline)	3 (1.2)	18 (7.2)	68 (27.3)	81 (32.5)
Partially Healed, n (% Baseline)	40 (16.1)	64 (25.7)	56 (22.5)	32 (12.9)
Unchanged, n (% Baseline)	186 (74.7)	151 (60.6)	102 (41.0)	84 (33.7)
Worse, n (% Baseline)	1 (0.4)	7 (2.8)	3 (1.2)	4 (1.6)
Not Readable, n (% Baseline)	19 (7.6)	8 (3.2)	14 (5.6)	6 (2.4)
Not Done, n (% Baseline)[d]	0	1 (0.4)	6 (2.4)	42 (16.9)
New Findings	19	17	3	3

TIO = tumour-induced osteomalacia.
[a] One subject discontinued from the study prior to Week 48.
[b] One subject discontinued from the study prior to Week 96.
[c] One subject discontinued from the study prior to Week 144, and 1 subject had not reached Week 144 as of the data cut-off date.
[d] Images were not done because the subject discontinued from study

At the last available post-baseline skeletal survey (performed at Week 144 for nine subjects, Week 72 for one subject, and Week 48 for one subject), the proportion of fractures/pseudofractures identified at baseline that graded as healed or partially healed was assessed by three readers.

Table 26: Active Fractures and Pseudofractures on Paired Baseline and Post-Baseline Skeletal Surveys - UX023T-CL201 (TIO Analysis Set)

	No. of Fractures/Pseudofractures (N = 14)		
	Reader 1	**Reader 2**	**Reader 3**
Baseline (n)	37	26	25
Last Post-Baseline Assessment, n (% of Baseline active fractures and pseudofractures)[a]			
Healed	17 (45.9)	17 (65.4)	10 (40.0)
Partially Healed	6 (16.2)	1 (3.8)	3 (12.0)
Unchanged	2 (5.4)	4 (15.4)	3 (12.0)
Worse	0	0	0
Not Readable	0	0	0
Not Done[b]	6 (19.4)	0	0
Missing[c]	6 (19.4)	4 (15.4)	9 (36.0)
New Fractures/pseudofractures on Last Skeletal Survey	6	0	18[d]

[a] Last available post-baseline skeletal survey was performed at Week 144 for nine subjects, Week 72 for one subject, and Week 48 for one subject.
[b] Post-baseline radiographs not available for 2 subjects, and one subject had not reached Week 144 as of the data cut-off date.
[c] Images were either not taken or not read.
[d] Eight of 18 fractures in three subjects were described by the reader as "old healed fractures." The reader had not identified these fractures on previous x-rays, and when he identified them on the last post-baseline skeletal survey, he graded them as healed. Therefore, the true number of new fractures/pseudofractures identified by this reader is 10.

In study KRN23-002, at baseline, 142 active fractures and 21 active pseudofractures were identified by bone scan (Table 27).

Table 27: Change from Baseline in Bone Condition assessed by 99mTc-labelled Bone Scan over Time

Parameter	Visit		KRN23 N = 13
Number of Active Fractures	Baseline	n	143
Graded Active Fracture	Week24	HEALED	2
		PARTIALLY HEALED	5
		UNCHANGED	126
		WORSE	1
		NEW FINDING	0
	Week48	HEALED	21
		PARTIALLY HEALED	23
		UNCHANGED	88
		WORSE	0
		NEW FINDING	0
Number of Active Pseudo Fractures	Baseline	n	21
Graded Active Pseudo Fracture	Week24	HEALED	0
		PARTIALLY HEALED	3
		UNCHANGED	18
		WORSE	0
		NEW FINDING	1
	Week48	HEALED	3
		PARTIALLY HEALED	5
		UNCHANGED	14
		WORSE	0
		NEW FINDING	0

Functional Mobility Tests

S*it-to-stand*- (STS) test: The STS-test measures lower extremity strength and mobility as a subject moves repeatedly from one position to another.

At baseline, 11 of the 14 subjects in the TIO Analysis Set completed the STS test; one subject did not perform the test at baseline because it was not part of the original protocol, one subject was unable to stand during the test due to lower extremity neuropathy, and testing was contraindicated in one subject due to injury/illness. Results for both studies are presented in Table 28.

6-Minute Walk (6MWT) Test: The 6MWT is frequently used to assess mobility. In Study UX023T-CL201, the 6MWT was performed for six of 14 subjects at baseline and eight of 14 subjects at Week 48. The low number of subjects was mainly due to inclusion of the 6MWT in the protocol in relation to the timing of the subjects' baseline visits. In Study KRN23-002, the 6MWT was performed for all 13 subjects at baseline and 12 of 13 subjects at Week 48.

Table 28: Mobility Assessments in Study UX023T-CL201 (TIO Analysis Set) and Study KRN23-002 (Efficacy Analysis Set)

Parameter	UX023T-CL201 (N = 14)		KRN23-002 (N = 13)	
Statistic	**Baseline**	**Week 48**	**Baseline**	**Week 48**
Mobility (6-minute Walk Test)				
n	6	8	13	12
Distance walked – mean (SD), meters	309 (210.5)	331 (174.7)	296 (96.0)	354 (116)
Change From Baseline - LS mean (SE)/ mean (SD)[a], meters	25.5 (16.58)		57.5 (42.8)	
p value	0.1241		-	
Percent predicted distance walked –mean (SD)	47.5 (30.81)	49.8 (25.52)	45.9 (14.7)	55.1 (17.4)
Lower Extremity Strength (Sit-to-Stand Test)				
n	11	12	12	11
Repetitions - mean (SD)	6.7 (3.95)	7.7 (4.54)	9.9 (4.5)	14.1 (4.0)
Change From Baseline, LS mean (SE)/ mean (SD) [a]	1.6 (0.50)		3.9 (4.2)	
p value	0.0012		-	

a: LS mean (SE) provided for Study UX023T-CL201 and mean (SD) provided for Study KRN23-002.

For comparison, for STS, a mean of 15 repetitions/30 sec was reported for 30 healthy controls (age 20–74 years) (Agarwal et al. 2006; Jones et al. 1999). For 6MWT, the mean (SD) distance walked at baseline was less than half of the predicted distance based on age and gender matched normative controls.

Pain, Fatigue, and HRQoL

The results from the Brief Pain Inventory (BPI), the Brief Fatigue Inventory and the SF-36v2 are given in Table 29, Table 30 and Figure 17. BPI-Q3 and BFI-Q3 refer to question 3 in the BPI and BFI scales, i.e., worst pain and worst fatigue, respectively, during the last 24 hours.

Table 29: Summary of BPI Assessments in Study UX023T-CL201 (TIO Analysis Set) and Study KRN23-002 (Efficacy Analysis Set)

BPI Parameter Statistic	UX023T-CL201 (N = 14)			KRN23-002 (N = 13)		
	Baseline	Week 48	Week 144	Baseline	Week 48	Week 72
BPI-Q3						
Mean (SD)	5.0 (3.16)	4.1 (3.09)	4.1 (2.69)	4.4 (2.6)	2.9 (2.9)	2.9 (2.7)
Change From Baseline, LS mean (SE)/Mean (SD)[a]	-	-0.90 (0.734)	-0.98 (0.643)	-	-1.3 (2.8)	-1.3 (2.1)
p value	-	0.2193	0.1268	-	-	-
Pain Severity						
Mean (SD)	3.9 (2.62)	3.0 (2.64)	3.1 (1.85)	3.1 (2.27)	2.5 (2.36)	2.5 (2.4)
Change From Baseline, LS mean (SE)/Mean (SD)[a]	-	-0.85 (0.665)	-0.94 (0.410)	-	-0.52 (1.88)	-0.53 (1.64)
p value	-	0.2031	0.0217	-	-	-
Pain Interference						
Mean (SD)	4.4 (3.15)	3.4 (3.38)	3.3 (2.82)	2.5 (2.27)	2.3 (2.64)	2.7 (2.63)
Change From Baseline, LS mean (SE)/Mean (SD)[a]	-	-1.04 (0.800)	-1.54 (0.616)	-	-0.21 (1.99)	0.19 (2.22)
p value	-	0.1942	0.0126	-	-	-

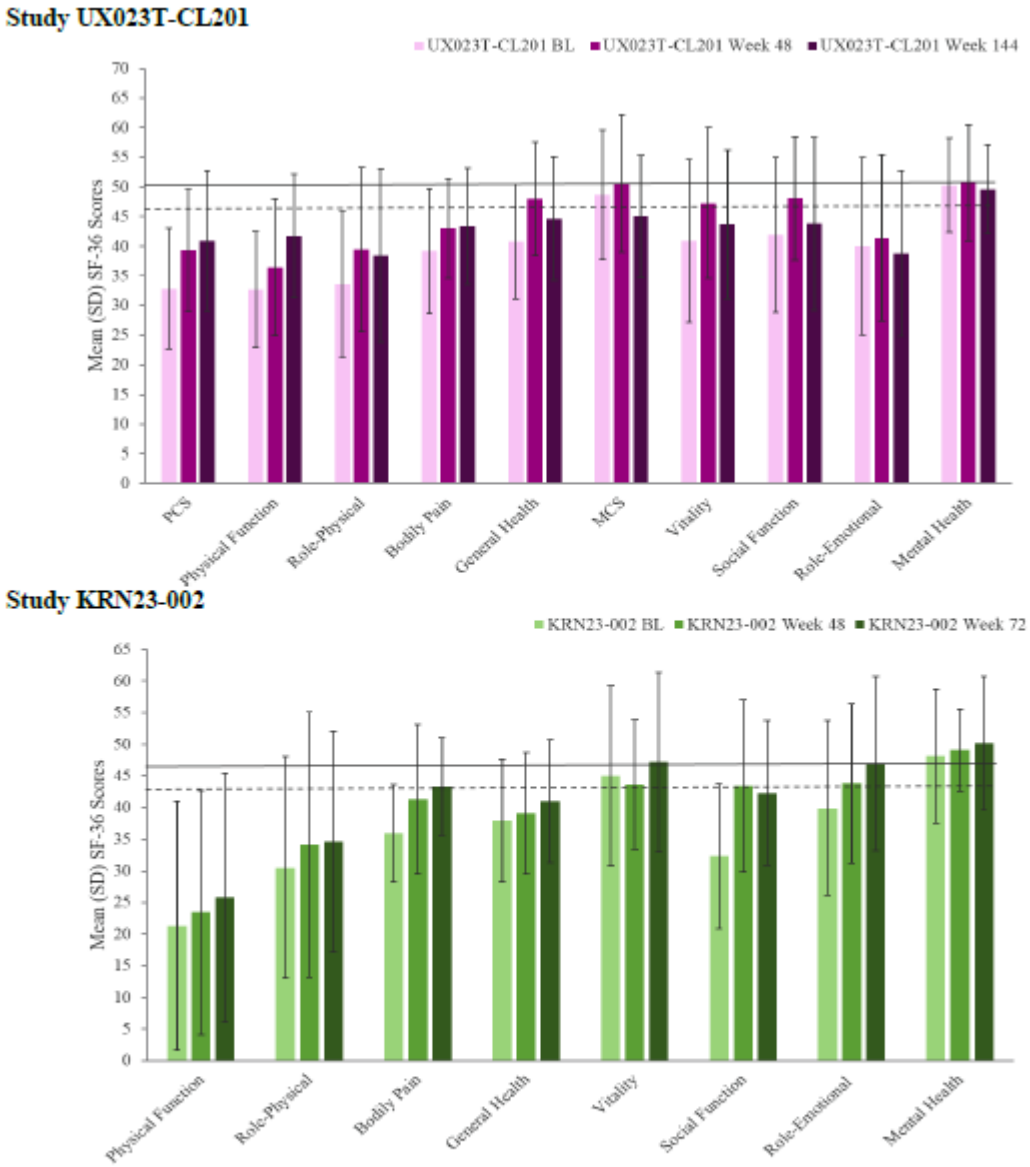
BPI-Q3 = Brief Pain Inventory – Question 3; LS = least squares; SD = standard deviation; SE = standard error; TIO = tumour-induced osteomalacia.
a: LS mean (SE) provided for Study UX023T-CL201, and mean (SD) provided for Study KRN23-002.

Table 30: Summary of BFI Assessments in Study UX023T-CL201 (TIO Analysis Set) and Study KRN23-002 (Efficacy Analysis Set)

BFI Parameter Statistic	UX023T-CL201 (N = 14)			KRN23-002 (N = 13)		
	Baseline	Week 48	Week 144	Baseline	Week 48	Week 72
BFI-Q3						
Mean (SD)	6.4 (2.81)	5.0 (3.79)	5.7 (2.0)	3.0 (2.6)	2.7 (2.2)	2.3 (2.3)
Change From Baseline, LS mean (SE)/Mean (SD)[a]	-	-0.84 (0.843)	-0.83 (0.598)	-	-0.5 (2.4)	-0.9 (2.2)
p value	-	0.3177	0.1649	-	-	-
Fatigue Severity						
Mean (SD)	6.2 (2.61)	4.4 (3.02)	5.0 (2.02)	3.3 (2.72)	3.1 (2.33)	2.5 (2.25)
Change From Baseline, LS mean (SE)/Mean (SD)[a]	-	-1.31 (0.558)	-1.22 (0.614)	-	-0.29 (2.23)	-0.95 (2.46)
p value	-	0.0192	0.0462	-	-	-
Fatigue Interference						
Mean (SD)	5.3 (2.60)	3.0 (3.23)	3.2 (2.48)	2.4 (2.52)	2.5 (2.77)	2.0 (2.20)
Change From Baseline, LS mean (SE)/Mean (SD)[a]	-	-1.85 (0.666)	-1.85 (0.495)	-	-0.03 (2.22)	-0.54 (1.77)
p value	-	0.0055	0.0002	-	-	-
Global Fatigue Score						
Mean (SD)	5.6 (2.54)	3.5 (3.0)	3.8 (2.20)	-	-	-
Change From Baseline, LS mean (SE)/Mean (SD)[a]	-	-1.64 (0.559)	-1.62 (0.453)			
p value	-	0.0034	0.0003			

BFI-Q3 = Brief Fatigue Inventory – Question 3; LS = least squares; SD = standard deviation; SE = standard error; TIO = tumour-induced osteomalacia.
a: LS mean (SE) provided for Study UX023T-CL201, and mean (SD) provided for Study KRN23-002.

Figure 17: HRQoL in Studies in Study UX023T-CL201 (TIO Analysis Set) and Study KRN23-002 (Efficacy Analysis Set)



BL = baseline; PCS = Physical Component Summary; MCS = Mental Component Summary; SD = standard deviation; TIO = tumour-induced osteomalacia; US= United States.
Note: The PCS comprises the Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP) and General Health (GH) domains. The MCS comprises the Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental Health (MH) domains. PCS and MCS scores are not available for Study KRN23-002.
Note: The solid line indicates the mean norm-based score for the general US or Japanese populations (< 50). Scores < 47 (dotted line) are indicative of impaired functioning (Maruish 2011).

Summary of main studies

The following tables (Table 31; Table 32) 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 31: Summary of Efficacy for trial UX023T-CL201

<table>
<tr><td colspan="4">Title: A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23, an Antibody to FGF23, in Subjects with Tumour-Induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS)-Associated Osteomalacia</td></tr>
<tr><td>Study identifier</td><td colspan="3">UX023T-CL201</td></tr>
<tr><td rowspan="5">Design</td><td colspan="3">Multicentre, open-label, Phase 2 study to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of burosumab (KRN23) in adult subjects with TIO or ENS-associated osteomalacia.</td></tr>
<tr><td colspan="2">Duration of main treatment phase:</td><td>48 weeks</td></tr>
<tr><td colspan="2">Duration of treatment extension phase:</td><td>252 weeks[a]</td></tr>
<tr><td colspan="2">Safety follow-up period:</td><td>12 weeks[b]</td></tr>
<tr><td colspan="3">a Total treatment duration of 300 weeks or until 31 Jan 2021, or until regulatory approval and commercial availability of burosumab, whichever is sooner.
b From last dose of study drug.</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Changes from baseline at Week 48 in histomorphometric indices osteoid thickness (O.Th), osteoid surface/bone surface (OS/BS), osteoid volume/bone volume (OV/BV) and mineralisation lag time (MLt)) were tested using a t-test if the normality assumption was valid. In this case, the null hypothesis tested was that mean change from baseline to Week 48 is 0. If the normal assumption was invalid, a sign test was used. In this case, the null hypothesis tested was that the median change from baseline to Week 48 is 0.</td></tr>
<tr><td>Treatment groups</td><td colspan="3">All subjects received subcutaneous (SC) burosumab treatment Q4W.
All subjects received SC burosumab treatment at a starting dose of 0.3 mg/kg. Doses were then titrated at Weeks 4, 8, 12, and 16 to achieve a fasting peak serum phosphorus level within the target range of 2.5 to 4.0 mg/dL. Titration was allowed to continue beyond the Week 16 visit if needed to achieve a dose that optimized trough serum phosphorus levels to within the normal range, to a maximum dose of 2.0 mg/kg Q2W.</td></tr>
<tr><td rowspan="3">Endpoints and definitions</td><td rowspan="2">Co Primary endpoints</td><td>Serum phosphorus levels</td><td>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, as averaged across dose cycles between Baseline and Week 24 (i.e., Weeks 2, 6, 10, 14, and 22).</td></tr>
<tr><td>Excess osteoid based on analysis of iliac crest bone biopsies</td><td>Change from baseline after 48 weeks in O.Th, OS/BS, OV/BV, and MLt.</td></tr>
<tr><td>Secondary endpoint</td><td>Serum phosphorus levels</td><td>• Proportion of subjects achieving mean serum phosphorus levels above 2.5 mg/dL (0.81 mmol/L) at the end of the dosing cycle (4 weeks after dosing), as averaged across dose cycles between baseline and Week 24.
• Mid-point of dosing cycle: mean change from baseline and percent change from baseline averaged across dose cycles between baseline and Week 24.
• End of dosing cycle: mean change from baseline and percent change from baseline averaged across dose cycles between baseline and Week 24.</td></tr>
</table>

			• Cumulative exposure: time-adjusted area under the curve (AUC) between baseline and Week 24.
	Secondary endpoint	Serum fibroblast growth factor 23 (FGF23), alkaline phosphatase (ALP), 1, 25 dihydroxy vitamin D ($1,25(OH)_2D$) and urinary phosphorus, tubular reabsorption of phosphate (TRP), and ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR)	Change from baseline over time.
	Secondary endpoint	Serum biochemical markers of bone turnover	Change and percent change from baseline over time in bone alkaline phosphatase (BALP), carboxy terminal cross-linked telopeptide of Type I collagen (CTx), procollagen type 1 propeptide (P1NP), and osteocalcin.
	Secondary endpoint	Muscle strength, functional mobility and lower extremity strength	Change from baseline over time in hand-held dynamometry (HHD), sit-to-stand (STS) test, weighted arm lift (WAL) test, and 6-minute walk test (6MWT).
	Secondary endpoint	Patient reported outcomes	Change from baseline over time in Brief Pain Inventory-Short Form (worst pain, pain severity, pain interference), Brief Fatigue Inventory (worst fatigue, fatigue severity, fatigue interference, global fatigue), and the 36-item Short Form Health Survey, version 2 (physical component scale, mental component scale, eight health domains).
Data cut-off	11 Jan 2019		
Results and Analysis			
Analysis Description	**Primary Analysis**		
Analysis population and time point description	Analysis groups included the TIO Analysis Set (all TIO subjects who received at least 1 dose of study drug) and the TIO Biopsy Analysis Set (all TIO subjects who received at least 1 dose of study drug and had paired bone biopsies at Baseline and Week 48). 11 January 2019 (cut-off date)		
Descriptive statistics and estimate variability	**Primary Endpoints**		
	Subjects with Mean Serum Phosphorus >LLN Averaged Across the Midpoints of the Dose Intervals		
	Treatment Group	TIO Analysis Set	
	Number of Subjects	14	
	n (%)	7 (50%)	
	95% CI	26.8, 73.2	
	Osteoid Thickness (µm)		

	Treatment Group		TIO Biopsy Analysis Set
	Number of Subjects		11
	Baseline, Mean (SE)		16.5 (3.63)
	Week 48, Mean (SE)		11.3 (2.77)
	Change from Baseline, Mean (95% CI)		-5.1 (-10.0, -0.2)
	Osteoid Surface/Bone Surface (%)		
	Treatment Group		TIO Biopsy Analysis Set
	Number of Subjects		11
	Baseline, Mean (SE)		56.8 (9.35)
	Week 48, Mean (SE)		56.6 (7.94)
	Change from Baseline, Mean (95% CI)		-0.2 (-13.9, 13.5)
	Osteoid Volume/Bone Volume (%)		
	Treatment Group		TIO Biopsy Analysis Set
	Number of Subjects		11
	Baseline, Mean (SE)		17.6 (5.88)
	Week 48, Mean (SE)		12.1 (4.65)
	Change from Baseline, Mean (95% CI)		-5.5 (-11.9, 0.9)
	Mineralisation Lag Time (Days)		
	Treatment Group		TIO Biopsy Analysis Set
	Number of Subjects		11
	Baseline, Mean (SE)		1598 (420)
	Week 48, Mean (SE)		940 (650)
	Change from Baseline, Mean (95% CI)		-565 (-2037, 907)
Effect estimate per comparison	Primary Endpoint	Comparison groups	Not applicable.
		P-value	Not applicable.
Analysis description	The proportion of subjects achieving mean serum phosphorus levels above 2.5 mg/dL was analysed with the Wilson score method. Both change from baseline and percent change from baseline on histomorphometric indices O.Th, OS/BS, OV/BV and MLt at Week 48 were tested using a t-test if the normality assumption was valid. If the normal assumption was invalid, a sign test was used. Statistical tests were 2-sided at the alpha = 0.05 significance level and 2-sided 95% CIs were used.		
Notes	MLt is considered of less value compared to the other bone biopsy markers as most values are imputed.		

Table 32: Summary of Efficacy for trial KRN23-002

Title: A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23 in Patients with Tumour-Induced Osteomalacia or Epidermal Nevus Syndrome		
Study identifier	KRN23-002	
Design	Multicentre, open-label, intraindividual dose-adjustment Phase 2 study to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of burosumab (KRN23) in adult subjects with TIO or ENS-associated osteomalacia.	
	Duration of main treatment phase:	140 weeks
	End of study	Week 144
Hypothesis	No formal hypothesis.	
Treatment groups	All subjects received subcutaneous (SC) burosumab treatment Q4W. All subjects received SC burosumab treatment at a starting dose of 0.3 mg/kg. Doses were then titrated at Weeks 4, 8, 12, and 16 to achieve a fasting peak serum phosphorus level within the target range of 2.5 to 4.0 mg/dL. Titration was allowed to continue beyond the Week 16 visit if needed to achieve a dose that optimized trough serum phosphorus levels to within the normal range, to a maximum dose of 2.0 mg/kg Q4W.	

Endpoints and definitions	Primary endpoint	Serum phosphorus levels	Serum phosphorus concentrations at each test timepoint.
	Secondary endpoint	Serum phosphorus levels	• When the mean of the mid-time points (Weeks 2, 6, 10, 14, and 22) of treatment cycles during the period from baseline to Week 24 was taken, whether or not the resultant mid-cycle mean serum phosphorus value achieved a level exceeding the lower limit (2.5 mg/dL [0.81 mmol/L]) of the normal range. • When the mean of the end (4 weeks after KRN23 administration) of each treatment cycle up to Week 48 was taken, whether or not the resultant end-cycle mean serum phosphorus value achieved a level exceeding the lower limit (2.5 mg/dL [0.81 mmol/L]) of the normal range. • Mid-time point of each dosing cycle: changes and percentage changes from baseline in the mean serum phosphorus for all mid-time points (Weeks 2, 6, 10, 14, and 22) of treatment cycles. • End of each treatment cycle up to Week 48: changes and percentage changes from baseline in the end-cycle mean serum phosphorus value obtained up to Week 48. • Changes from baseline at each test time point.
	Secondary endpoint	Histomorphological changes	Percentage change from baseline at Week 48 in O.Th, OS/BS, OV/BV, and MLt.
	Secondary endpoint	Serum fibroblast growth factor 23 (FGF23), alkaline phosphatase (ALP), 1, 25 dihydroxy vitamin D ($1,25(OH)_2D$) and urinary phosphorus, tubular reabsorption of phosphate (TRP), and ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR)	Change from baseline over time.
	Secondary endpoint	Serum biochemical markers of bone turnover	Change and percent change from baseline over time in bone alkaline phosphatase (BALP), carboxy terminal cross-linked telopeptide of Type I collagen (CTx), procollagen

			type 1 N propeptide (P1NP), and osteocalcin
	Secondary endpoint	Muscle strength, functional mobility and lower extremity strength	Change from baseline over time in hand-held dynamometry (HHD), sit-to-stand (STS) test, weighted arm lift (WAL) test, and 6-minute walk test (6MWT)
	Secondary endpoint	Patient reported outcomes	Change from baseline over time in Brief Pain Inventory-Short Form (worst pain, pain severity, pain interference), Brief Fatigue Inventory (worst fatigue, fatigue severity, fatigue interference, global fatigue), and the 36-item Short Form Health Survey, version 2 (physical component scale, mental component scale, eight health domains).
Database lock	13 July 2018		
Results and Analysis			
Analysis Description	**Primary Analysis**		
Analysis population and time point description	The Efficacy Analysis Set (FAS) included all TIO subjects who received at least 1 dose of study drug and had serum phosphate data obtained. 3 May 2018 (cut-off date)		

Descriptive statistics and estimate variability	**Primary Endpoint**	
	Serum Phosphorus Concentrations at Each Test Timepoint (mg/dL)	
	Treatment Group	TIO
	Baseline, n, Mean (SD)	13, 1.62 (0.49)
	Week 1, n, Mean (SD)	13, 2.20 (0.89)
	Week 2, n, Mean (SD)	13, 2.28 (0.95)
	Week 4, n, Mean (SD)	12, 1.94 (0.87)
	Week 6, n, Mean (SD)	13, 2.62 (1.00)
	Week 8, n, Mean (SD)	13, 2.27 (0.72)
	Week 10, n, Mean (SD)	13, 2.60 (0.93)
	Week 12, n, Mean (SD)	13, 2.44 (0.80)
	Week 14, n, Mean (SD)	13, 2.75 (0.96)
	Week 16, n, Mean (SD)	12, 2.52 (0.68)
	Week 20, n, Mean (SD)	12, 2.51 (0.58)
	Week 21, n, Mean (SD)	12, 2.90 (0.69)
	Week 22, n, Mean (SD)	12, 3.04 (0.72)
	Week 24, n, Mean (SD)	12, 2.65 (0.62)
	Week 28, n, Mean (SD)	12, 2.62 (0.62)
	Week 32, n, Mean (SD)	12, 2.62 (0.52)
	Week 36, n, Mean (SD)	12, 2.65 (0.47)
	Week 40, n, Mean (SD)	11, 2.65 (0.57)
	Week 44, n, Mean (SD)	12, 2.63 (0.61)
	Week 48, n, Mean (SD)	11, 2.70 (0.44)
	Week 56, n, Mean (SD)	12, 2.63 (0.61)
	Week 64, n, Mean (SD)	11, 2.70 (0.69)
	Week 72, n, Mean (SD)	12, 2.73 (0.39)
	Week 80, n, Mean (SD)	12, 2.75 (0.49)
	Week 88, n Mean (SD)	11, 2.72 (0.43)

	Secondary Endpoints		
	Osteoid Thickness (µm)		
	Treatment Group		TIO
	Number of Subjects		3
	Baseline, Mean (SD)		16.03 (13.67)
	Week 48, Mean (SD)		13.50 (7.05)
	Change from Baseline, Mean (SD)		-2.53 (8.18)
	Osteoid Surface/Bone Surface (%)		
	Treatment Group		TIO
	Number of Subjects		3
	Baseline, Mean (SD)		47.7 (23.1)
	Week 48, Mean (SD)		43.0 (5.6)
	Change from Baseline, Mean (SD)		-4.7 (19.8)
	Osteoid Volume/Bone Volume (%)		
	Treatment Group		TIO
	Number of Subjects		3
	Baseline, Mean (SD)		14.03 (15.23)
	Week 48, Mean (SD)		9.23 (5.48)
	Change from Baseline, Mean (SD)		-4.8 (10.14)
Effect estimate per comparison	Primary Endpoint	Comparison groups	Not applicable.
		P-value	Not applicable.
Analysis description	Descriptive statistics		
Notes	Bone biopsy data from this study is considered less robust as data is available for three subjects only and there were large variation in baseline data.		

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies.

The efficacy of burosumab in adults with Tumour Induced Osteomalacia (TIO) was evaluated in two small, open-label Phase 2 studies (UX023T-CL201 in the USA and KRN23-002 in Japan and Korea). No clinical studies were performed in paediatric subjects with TIO.

In total, not more than 27 subjects were enrolled in the two studies in the application to extend the indication for Crysvita to include treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised, in patients aged 1 year and over. The sample size is very limited, based on the rareness of the condition. Further, there is a substantial heterogenicity among subjects with TIO. Differences in disease severity and duration, levels of FGF-23, dosing, and compliance with oral phosphate/active vitamin D treatment prior to study entry contribute to this heterogenicity. This is likely have contributed to the complexity of the study results.

The data cut-off for the initial submission was January 2019 for UX023T-CL201 and May 2018 for KRN23-002, corresponding to data from Week 144 and Week 88, respectively. Upon request, the MAH has presented data up to End of Study (EoS) for both studies. Study UX023T-CL201 collected data to Week 300; however, only one patient completed treatment of this duration. Study KRN23-002 collected data up to Week 216 (n=2). Data beyond Week 240 (n=7) for study UX023T-CL201 and beyond Week 184 (n=5) for KRN23-002 cannot be considered robust.

According to the provided Subject disposition for study UX023T-CL201, in total six subjects discontinued the study. However, the MAH notes that although study UX023T-CL201 collected efficacy data to Week 300, only one patient completed treatment of this duration, indicating that seven subjects discontinued study treatment but stayed in the study. A similar pattern could be suspected in study KRN23-002, as data from only three subjects are presented towards the end of the study.
It is considered of some concern that only 4/27 subjects seem to adhere to treatment until the end of the studies. Upon request, the MAH has clarified that this was in large part due to that per study protocol, the study duration differed depending on whether subjects transitioned off the study to receive commercial burosumab treatment when it became available in their territory. For the remaining subjects discontinuing the study, it is agreed with the MAH that the vast majority could be considered unrelated to treatment.

Posology

In the posology for the TIO indication in adults, the MAH proposed the same starting dose as used in the studies, i.e., 0.3 mg/kg Q4W, and a maintenance dose up to 2 mg/kg Q4W (maximum absolute dose per administration 180 mg) or even 2 mg/kg Q2W.
The approved starting dose for adult subjects with XLH is 1 mg/kg. No maximum weight-based dose in adults with XLH is provided in the SmPC; however, the maximum dose per administration is 90 mg, restricting the dose to approximately 1.3 mg/kg in a subject weighing 70 kg. The higher proposed maximum dose for TIO subjects is based on the argumentation that the serum concentration of FGF-23 is typically higher in subjects with TIO than with XLH, which may warrant a higher dose of burosumab. This is in line with the baseline FGF-23 levels in studies UX023T-CL201 and KRN23-002 compared to the pivotal study in adult XLH subjects. In total, in UX023T-CL201, seven subjects (50%) were administered doses over 100 mg, i.e., above the maximum approved dose per administration in adult XLH subjects (90 mg). This may support that a higher dose than the maximum approved dose in the adult XLH population may be needed in some subjects with TIO-induced hypophosphataemia.

Despite the relatively high maximum doses allowed in the studies, the actual dosing was quite conservative. The mean burosumab dose at all time points in both studies was below the recommended starting dose for adults with XLH. In Study KRN23-002, no subject was given a higher dose than 1.8 mg/kg and no subject was administered 180 mg on any occasion. In Study UX023T-CL201, only one subject used the maximum dose (2 mg/kg); however, another subject also reached the maximum absolute dose of 180 mg. For one subject (the subject given the 2 mg/kg dose), the option to administer burosumab Q2W was used.
Three subjects in the TIO-population did not reach LLN for serum phosphate. One subject was given the maximum allowed study dose, 2 mg/kg Q2W and reaching the maximum absolute dose, 180 mg per administration, whereas the other two subjects did not receive maximal treatment. Of note, these three subjects had unusually high baseline FGF-23. One subject had the highest baseline level of FGF-23 across the TIO studies. One subject had the highest baseline level of FGF-23 in Study UX023T-CL201 whereas one subject reported an elevated level at baseline (well above the study mean of 770 pg/mL). This may explain the (partial) lack of response in these subjects.
The lower starting dose in the TIO studies compared to the approved starting dose in adults with XLH is related to the studies being launched before the approval of Crysvita in adults. It could be argued that a lower starting dose compared to the adult XLH population is somewhat contradictory given the assumption that a higher maintenance dose may be needed in the TIO population. However, over 20% of the subjects in both studies were given ≤0.3 mg/kg burosumab at each time point, indicating that this dose may be sufficient in some subjects.
The somewhat conservative dosing in the TIO-population is considered prudent and in line with the recommendation in section 4.4 of the approved SmPC, that the serum phosphate levels with burosumab

treatment should be targeted in the lower part of the normal range to avoid events of hyperphosphataemia.

As Study KRN23-002 proceeded, more patients needed to receive the higher doses of burosumab to maintain serum phosphorous above LLN. No neutralising ADAs, which could otherwise be an explanation to lack of efficacy over time, have been reported in either of the TIO studies. The MAH argues that it is feasible that at least some subjects experienced tumour progression with accompanying increased levels of FGF23 as the study continued. This is accepted.

The relative maximum dose 2mg/kg Q2W is approved in the paediatric XLH population up to the age of 18 years. Notwithstanding, according to the proposed SmPC, the maximum dose per administration in the adult TIO population is substantially higher compared to the currently approved maximum dose in adult XLH subjects, i.e., 180 mg Q2W compared to 90 mg Q4W. Few patients has nevertheless been exposed to these high levels. This is further discussed in the safety section.

The clinical studies enrolled only adult subjects. The dosing regimen for this paediatric population was evaluated by modelling and simulation that extrapolated adult population PK and PK/PD models to paediatric age groups. It is reasonable to assume that the PK/PD of burosumab would be similar in paediatric patients to that in adult patients with TIO, and that any potential differences in the PD relationship between adults and paediatrics is likely to be captured by the proposed weight-based posology of burosumab. The proposed starting dose in the paediatric population is 0.4 mg/kg for subjects ≤12 years of age and 0.3 mg/kg for subjects >12 years of age compared to 0.8 mg/kg in the paediatric XLH population (1-17 years), whereas the maximum dose in paediatric subjects with TIO is identical to the maximum dose in the approved paediatric XLH population, 2 mg/kg Q2W, but not more than 90 mg per administration. Similar to the proposed starting dose in adult TIO patients, the starting dose in paediatric TIO patients is lower compared to XLH dosing recommendation.

Given careful titration of the dose based on phosphorus levels, the dosing recommendation in adult and paediatric TIO patients could be accepted (please refer also to the safety section).

Study design

Overall study design

Both studies were open-label and single-armed. The studies were not designed to show efficacy against standard of care for the condition. The lack of comparator is considered a major weakness with the TIO development program. Daily oral treatment with Vitamin D and/or phosphate is considered standard of care (SoC) for TIO when surgery is not feasible and was also used by in principle all participants before inclusion in the studies. No relevant comparison between burosumab and SoC can be made with the current study design.

It is not agreed with the MAH that a randomised, controlled study in the TIO population would not have been feasible. It is agreed that a blinded, placebo-controlled design would have been challenging; nevertheless, a randomised controlled study using delayed design, i.e., with half of the subjects randomised to receive burosumab from baseline and the other half to start with SoC for a 3-6-months before transition to burosumab, could have been considered. As both studies are now concluded, this is not further pursued.

The MAH argues that the lack of control group could be compensated by the vast majority of subjects being treated with Vitamin D and/or phosphate before entering the study. This is not agreed. Per the study protocols, active treatment with oral phosphate substitution and active Vitamin D should be withdrawn at least two weeks prior to the screening visit. As such previous treatment was not an eligibility criterion for the studies, no earliest time for withdrawal of conventional therapy was identified. In Study UX023T-CL201, subjects were without oral phosphate and vitamin D therapy for at least 6

weeks, and in Study KRN23-002, subjects were without oral phosphate and vitamin D treatment for at least 8 weeks. However, actual screening periods varied for each subject.
Oral phosphate is normally given 3-5 times daily, as serum phosphate is rapidly regulated in the body, precluding that serum phosphate levels would be sustained several weeks or months after withdrawal of conventional therapy.

The MAH has provided a summary of the last regular serum phosphate measurement before entering the study for comparison to study measurements (for details, please refer to Response to Question 23). Data is difficult to interpret as regular measurements were only available for in total 17 subjects (UX023T-CL201: n=8; KRN23-002: n=9), the time between the last regular serum phosphate measurement and the baseline measurements varied greatly, and, at least in study UX023T-CL201, this time was generally several months long. Furthermore, only one pre-withdrawal phosphate measurement was available for each subject. Nevertheless, a numerical decrease in mean serum phosphate was seen between last regular measurement and baseline, from 2.2 mg/dL to 1.8 mg/dL in UX023T-CL201 and from 2.3 mg/dL to 1.6 mg/dL in KRN23-002 for the same 17 subjects, in support of the view that baseline measurements could not be considered on treatment.

As the phosphate co-primary analysis in study UX023T-CL201 was not a comparison to baseline phosphate levels, this is not considered to impact the primary endpoint. For KRN23-002, the primary endpoint was "Serum phosphorus concentrations at each test timepoint"; however, only descriptive statistics were applied. The MAH has presented updated graphs in section 5.1 of the SmPC**.**

Notwithstanding, many TIO patients have limited effect of active Vitamin D and/or oral phosphate. Furthermore, as pointed out above, conventional treatment is administered as multiple daily doses, associated with high non-compliance in both adults and children that compromise their overall tolerability long term. Treatment is often associated with potential risks such as nephrocalcinosis, hypercalciuria and secondary hyperparathyroidism. The beneficial effect of burosumab on phosphate homeostasis in the TIO population is therefore considered of clinical relevance also in the absence of a comparator and a positive treatment effect compared to baseline may still form a support for the applied indication.

One subject underwent tumour resection during the first 24 weeks of Study UX023T-CL201. After surgery, serum phosphate temporarily increased from 1.3 mg/dL to 3.0 mg/dL, but his average serum phosphate level remained below the lower limit of normal at Week 24 with unchanged dose of burosumab. The subject was a non-responder at Week 24 and tumour surgery in this single subject is therefore not considered to have affected the primary endpoint.

Eligibility criteria

The eligibility criteria restrict inclusion to subjects with TIO-associated osteomalacia that was not amenable to cure by surgical excision of the underlying tumour/lesion, either due to the location of the tumour or inability to locate the lesion. This reflects the condition described in the MAH's proposed amendment to the wording in SmPC section 4.1.

Study UX023T-CL201 enrolled subjects from the US, whereas Study KRN23-002 enrolled subjects from Japan and South Korea. To address the concern whether the results from the studies are applicable to the European population, the MAH provided a comparison across two recently published case series from China and Italy, showing that the clinical presentation of the patients from these two diverse ethnicities was almost identical. It is therefore unlikely that there is any clinically meaningful difference in disease presentation between the study populations and the European population.

Endpoints

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 (2 weeks after dosing), as averaged

across dose cycles between Baseline and Week 24 was a co-primary endpoint in Study UX023T-CL201. This endpoint was identical to the primary endpoint in Study UX023-CL303, the pivotal study in adults with XLH, assessed in procedure EMEA/H/C/004275/II/0010/G.
The primary endpoint in Study KRN23-002 was serum phosphate concentration at each test time point. The primary endpoint was entirely descriptive. Serum phosphate concentration averaged across the midpoint of dose cycles and over the endpoint of dose cycles (Weeks 0 – 24) were secondary endpoints in UX023T-Cl201. In both studies, serum phosphate peaks (i.e., midpoint of the dose interval, 2 weeks post-dose) and troughs (i.e., endpoint of the dose interval, 4 weeks post-dose) were assessed up to Week 22, after which only troughs were assessed.

In procedure EMEA/H/C/004275/II/0010/G, it was considered that the strong correlation between serum phosphorus levels and the symptomatology in XLH justified the use of this pharmacodynamic surrogate marker as primary efficacy endpoint. As the pathophysiology in XLH and TIO both involve elevated levels of FGF-23 with subsequent hypophosphataemia, this endpoint could be considered adequate also for evaluation of burosumab in TIO.

Osteomalacia, characterised by softening of bone tissue due to defective mineralisation of osteoid demonstrated by excessive osteoid thickness, volume, and surface, is a main feature of TIO. Osteomalacia may be associated with symptoms as body pains, muscle weakness, and fragility of the bones. The change from Baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of burosumab treatment using the histomorphometric indices osteoid volume/bone volume (OV/BV), osteoid surface/bone surface (OS/BS), osteoid thickness (O.Th) and mineralisation lag time (Mlt) was the second co-primary endpoint in Study UX023T-CL201. Upon request, the MAH has clarified that there is no minimal change from baseline that could be considered clinically relevant. Instead, the reduction in excess osteoid becomes clinically relevant through the subsequent improvements in bone and joint pain, fractures, stiffness and physical function.

Although the excess osteoid endpoint consists of 4 indices, each was analysed independently. The classification of "co-primary" in the context of MAA is interpreted as if all five must achieve some pre-specified statistical and/or clinical criteria. As no pre-specified statistical criteria were defined, statistical inference that fully controls the type I error is problematic. In their reply, the MAH discussed, hence in retrospect, what could have been a suitable approach to control the type I error. This is however a post-hoc construction. Study UX023T-CL201 had five *co*-primary endpoints and only if the study was to have been viewed as successful only if all five were successful in some sense, no multiplicity consideration had been necessary, at least not for the primary endpoints and the criticism regarding lack of a pre-defined study success criterion may not have emerged.

Fractures/pseudofractures were assessed by two complementary methods (whole body bone scans, using 99mTc-labeled methylene diphosphonate, and standard radiographs [skeletal survey]). To reduce the risk of bias, initial lesions locally identified by bone scan or skeletal surveys at baseline were followed by central readers (one for bone scans, three for skeletal surveys) blinded to subject data.
Bone fractures and pseudofractures were assessed as exploratory objectives only. However, the clinical relevance of these findings is easier to interpret than bone histology. Moreover, fracture data is considered less susceptible than serum phosphate measurements to the gap in treatment after terminating standard of care before screening. Therefore, this data could potentially support the proposed new indication.
As previously pointed out, the risk of bias is considered substantial if the radiographs with the reader knowing that a certain set of radiographs represented before and after treatment in the same subject. Upon request, the MAH has undertaken a re-read of all available images (bone scans and X-rays) by an independent reading centre. Images were assessed without reference to baseline images and were provided to the reader in a random order. The reader was tasked with assessing each bone scan and X-ray to identify the presence of fractures or pseudofractures.

Three patient-reported scales were used to evaluate pain, fatigue and quality of Life (HRQoL): Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI) and SF-36v2. The three scales have been evaluated for relevance in adult TIO and assessed for validity, reliability and sensitivity to change in a Patient-reported Outcomes Dossier for Patients with Tumour-induced Osteomalacia provided by the MAH. In this evaluation, it was concluded that the PRO instruments were supported as secondary endpoints in the Phase 2 trials of burosumab in TIO. However, due to the sample size, it was recommended that the results should generally be considered exploratory. P-values provided by the MAH are therefore not taken into consideration.
The MAH points out that TIO subjects were without treatment for approximately 6 weeks before baseline assessments. It is possible that withdrawal of an effective treatment could worsen physical performance and reported HRQL at baseline. Moreover, the open-label design does not account for expectation effects in these subjective PRO measures, and it is difficult to estimate a true effect of a drug itself. The MAH addressed this by comparing BPI and BFI data from subjects treated with placebo in XLH Study UX023-CL303 (available from baseline to Week 24) with corresponding data from subjects enrolled in TIO Study UX023T-CL201. This is considered a rational approach; however, only two post-baseline observations were available for comparison for the XLH placebo population and an impact of the open label design on the PRO data could not be ruled out. Therefore, data should be interpreted with caution.

Statistical analysis

The open label nature of both studies without an adequate control in a small number of patients where a priori statistical criteria of success had not been clearly defined in the presence of potential confounding were, and still are, major deficiencies that limits interpretation of the primary and secondary endpoints efficacy results. The resulting inferences from the provided study data can only be considered as preliminary and not confirmatory. This conclusion has not changed albeit will not be further pursued.

While it is acknowledged that this is a rare condition, the internal validity of the trial is questionable, and an inadequately planned design and analysis cannot substitute a well-planned analysis (and trial design). The logical consequence for this is that without knowing the extent of the type I error associated with a conclusion that the experimental treatment may confer benefit, the Applicant has failed to quantify the chance of that of an erroneous that may affect future patients who may be given the experimental intervention.

The Applicant has justified the TIO study design including prior statistical criteria and type I error control. For none of the studies was there a prospective discussion on a minimum required level of efficacy for the study to be interpreted as successful. In their reply, the MAH mainly reiterated the non-justified assumptions made what regards study UX023T-CL201 sample size and underlined that the study KRN23-002 sample size was ultimately decided based on enrolment feasibility. This could be understood in the context of that each study was planned in the setting of being the first in the current patient population, and in that the analyses were to provide descriptive summaries that, taken together, rather witness of proof-of-concept and hypothesis generation. The MAH invokes the rare patient population and the highly heterogeneous clinical presentation. This is acknowledged, but unfortunately, offers no reassurance but rather underlines the importance of pre-defined, substantiated, and justified hypotheses. The deficiency pertaining to lack of pre-defined success criteria is by default rather futile to address in retrospect.

Further, the MAH clarified that study UX023T-CL201 analyses were conducted without any consideration concerning multiplicity and discuss, hence in retrospect, what could have been a suitable approach to control the type I error. Although the now proposed method, a stepwise procedure combined with Bonferroni, is per se acceptable this is a post-hoc construction. The MAH claims that by using the proposed method, the conclusions from the analysis of co-primary efficacy endpoints do not change. It appears however that it could be questioned that the confidence interval for osteoid thickness would not contain 0 if the method of Bonferroni was actually to be applied. Irrespective of which, with the outcomes

already at hand, any attempt to justify a non-predefined approach for type I error control owns little (if anything) of value.

Regarding potential confounding the MAH's reply was initially far from adequate, and the applicant was requested, for both studies (KRN23-002 and UX023T-CL201), to again address the impact of confounding on the observed results, in particular the primary and secondary outcome. The MAH has now provided some evidence of the impact of covariates/potential confounders on outcomes. The analyses do not provide an equivalent estimate of a treatment effect in the context of comparative evidence due to the limitation of the design, being a single arm trial. Consequently, the matter is partially resolved, but not pursued further as definitive evidence of an unbiased effect as a consequence of confounding would be very difficult to derive. However, the main evidence is not foremost based on the two submitted single arm TIO trials but mainly relies on that it is possible to extrapolate to earlier XLH studies.

To compare the burosumab treatment effect across XLH and TIO, the MAH conducted propensity score matched analyses using study UX023T-CL201 and adult XLH Study UX023-CL303. However, a justification for assumptions around propensity score modelling has not been adequately provided (propensity score modelling requires a non-zero probability of patients receiving the new (experimental) treatment). Moreover, in this specific case, such analyses are not considered to add any information on the effect of burosumab on serum phosphate levels. Therefore, no close attention is paid to the propensity score modelling.

Study analyses were initially to provide descriptive summaries and given the absence of a concurrent control group; they pertain to baseline comparisons. In outcome summaries, subjects with missing data were excluded. This is considered an additional source of potential bias and an intent-to-treat approach had been preferred. Given that it was only one or two subjects with missing data up to week 24/48 and that outcomes are interpreted in a descriptive fashion, this was not further pursued. For study KRN23-002, a plot depicting individual phosphorus values over time had been presented and given the limited data sets, this was considered illustrative, and a corresponding figure was requested also for study UX023-CL201. Although individual values are not that easy to follow, fluctuations are evident. Over time, the majority appears to lie above the lower limit of normal (2.5 mg/dL) but then there are not that many subjects that contribute with data. This is not further pursued.

Study conduct

The date of first signed informed consent for Study UX023T-CL201 was 24 March 2015 and the SAP version 1.0 was dated 04 May 2016. From the summaries of the five amendments provided by the MAH, it seems as there have been alterations to the co-primary endpoints after study start (Amendment 2 dated 14 October 2015, Amendment 4 dated 10 November 2017). The MAH has clarified that at the time of the second amendment, only two subjects were included in the study, one with 4 weeks of dosing and one with 24 weeks of dosing. A sensitivity analysis excluding data from these two patients confirmed that there was no impact on the results from this amendment.

Based on the ongoing XLH bone biopsy study UX023-CL304, Amendment 4 from November 2017 introduced absolute change from baseline in histomorphometry measurements in place of a relative, percent change from baseline as analysis of the co-primary bone histology endpoint. Both the absolute change from baseline and the percent change from baseline are presented in Table 2. Alterations to a primary endpoint in the end of an open label study is questionable, as this may compromise the integrity of the study. Notwithstanding, the study is already concluded, and this could not be addressed in retrospect.

According to the Study UX023T-CL201 SAP, administrative analyses were to be performed to support e.g., product development per the Sponsor's decision. The seemingly relaxed view when it comes to

performing interim analyses and present outcomes was considered to add to concerns regarding study integrity albeit was not pursued.

Further, a rare disease may alone not necessarily justify a very limited sample size and initially the sample size in each study was foremost understood to pertain to the phase 2 context. However, it can be agreed with the MAH that the rareness of the condition hampers recruitment. As an example, almost one third (9/28) of all Japanese subjects with TIO aged >18 years were included in Study KRN-002. Taken this into consideration, the difficulty to increase the sample size is acknowledged. Originally study UX023T-CL201 was planned as a single centre study and was to include approximately 6 subjects. With amendment 1 this became a multi-centre study and with amendment 2, after the study had started, the sample size was increased to approximately 15 adult subjects. In the end, a total of 17 subjects were enrolled, (see further below). For study KRN23-002 the sample size was decided based on feasibility. In the end, 14 subjects, all with TIO, were enrolled to be compared with expected six.

Two of the subjects enrolled in Study UX023T-CL201 were later (after Week 48) found to have XLH. These subjects are not included in the TIO analysis set. Genetic testing for the PHEX mutation was introduced late in study UX023T-CL201, which explains why the two subjects with XLH were not identified earlier. XLH is a genetic disorder with complete penetrance and clinical signs of the disease normally develop in early childhood. Severity varies between individuals, but it is not likely from the pathophysiology of the disease that an asymptomatic subject with XLH would suddenly develop severe symptoms in adult age. Genetic testing for PHEX mutations only in patients, whose symptoms of hypophosphatemia began in childhood and whose tumour could not be located, is considered adequate to exclude patients with XLH. According to the MAH, all subjects in both studies fulfilling these criteria were tested without identification of additional subjects with XLH.

After removal of the subjects with ENS and XLH, the TIO Analysis Set in Study UX023T-CL201 consists of 14 subjects. Three of these subjects discontinued the study before Week 144: One subject experienced a fatal event, one subject discontinued burosumab treatment due to serious TEAE and was subsequently discontinued from the study due to lack of phosphorus increase in response to burosumab pursue chemotherapy treatment of the underlying tumour and one subject was discontinued from the study by the Sponsor/Investigator due to low burosumab dose with intermittent administration.
No screening phosphate level was provided for this subject; however, the day before the first dose, serum phosphate was above the upper level for inclusion in the study (2.5 mg/dL). It is highly questionable whether this subject should have been included in the study, given that serum phosphate the day before first treatment was within the normal range.
It is not considered accurate for the Investigator/sponsor to actively remove subjects from the statistical analyses during the study, especially not in a single arm, open label study. Notwithstanding, data from all 14 TIO subjects seem to have been included in the Week 24 analyses. The issue is therefore not further pursued.

Fourteen subjects enrolled in Study KRN23-002, all with TIO. One of the subjects withdraw consent before exposure to burosumab. No further information about this subject was provided. The subject was not included in the safety or efficacy analysis sets, which therefore include 13 subjects.

Efficacy data and additional analyses

Efficacy was evaluated in the UX023T-CL201 TIO analysis set (N=14) and the KRN23-002 Efficacy analysis set (N=13). Except for country of origin and weight, the study populations in the two studies were similar.

Results from the two studies were not pooled; however, integrated analyses were performed based on pooled efficacy data available through Week 88 from the two studies. It is agreed with the MAH that the similarity in study design, study population and endpoint allow for an integrated analysis.

Direct comparisons to the efficacy in adult XLH studies are hampered by differences in study populations, study design and underlying disease. However, to get an estimation on the effect size in the TIO development program, results from the adult XLH development program, in particular from the pivotal study UX023-CL303 and the adult bone biopsy study UX023-CL303, are sometimes included in the following discussion. The adult XLH-studies were assessed in procedure EMEA/H/C/004275/II/0010/G.

Phosphate endpoints

In both TIO studies, mean baseline serum phosphate was 1.6 mg/dL (0.5 mmol/L).

A total of 50% (95% CI: 26.8, 73.2) of the subjects in the TIO analysis set had achieved Mean Serum Phosphorus Levels > 2.5 mg/dL, i.e., over the lower limit of normal (LLN), as averaged across the mid-point of the dose intervals (i.e., 2 weeks after dosing) between Baseline and Week 24 (Co-primary endpoint in Study UX023T-CL201). In comparison, 94% of the burosumab treated population in the adult XLH-study UX023-CL303 achieved this endpoint.

In Studies UX023T-CL201 and Study KRN23-002, serum phosphate averaged across the midpoint of dose cycles was 2.64 and 2.63 mg/dL (0.85 and 0.85 mmol/L) respectively, for Week 0-24, compared to 3.24 mg/dL (1.05 mmol/L) in UX023-CL303.

As discussed elsewhere, the actual dosing show that most subjects in UX023T-CL201 and KRN-002 were given doses well below the allowed maximum dosing in the studies, indicating that dosing in the TIO population was conservative. This, together with a difference in baseline serum phosphate levels between the studies (1.6 mg/dL [0.5 mmol/L] in UX023T-CL201 and KRN23-002 versus 2.0 mg/dL [0.65mmol/L] in UX023-CL303) is considered to at least in part explain the differences in outcome between the two populations. As data indicate that the 0.3 mg/kg starting dose is sufficient for some patients, both in the clinical studies and the post-marketing data from the US and Japan, the conservative starting dose is considered prudent and in line with the recommendations to avoid hyperphosphataemia.

The beneficial effect of burosumab was sustained throughout the studies. In study UX023T-CL201, serum phosphate had increased from 1.60 mg/dL at baseline to 2.56 mg/dL at Week 144. The corresponding value at Week 240 (n=7) was 2.57 mg/dL. In KRN23-002, baseline serum phosphate was 1.62 at baseline, 2.72 at Week 88 and 2.70 mg/dL at Week 176 (n=8). No statistical analyses after Week 144/88 were performed.

In summary, it is agreed with the MAH that burosumab treatment resulted in an increase in serum phosphate compared to the baseline level; however, somewhat more modest when compared the adult XLH population, which, at least in part may be a question of dosing. This increase is considered to be of clinical relevance and may offer a support for the applied indication.

Bone biopsy histomorphometry

The change from Baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of burosumab treatment using the histomorphometric indices osteoid volume/bone volume (OV/BV), osteoid surface/bone surface (OS/BS), osteoid thickness (O.Th) and mineralisation lag time (Mlt) was the second co-primary endpoint in Study UX023T-CL201. A similar endpoint was used in the adult XLH bone biopsy study UX023-CL304, with interim data assessed in procedure EMEA/H/C/004275/II/0010/G. In general, osteomalacia was more pronounced in Study UX023-CL304.

In Study UX023T-CL201, there was a numerical improvement compared to baseline in OV/BV (-5.5 [-11.9, +0.9] %; p=0.086) and O.Th (-5.1 [-10, -0.2] um; p=0.048). The percent change from baseline

for OV/BV was 31% and for O.Th 32%. The corresponding percent change from baseline in the XLH population was 54% and 33%, for OV/BV and O.Th, respectively. However, unlike UX023-CL304, no improvement was seen in OS/BS in study UX023T-CL201 (-0.2 [-14, +14] %, p=0.98) (-26% and -0.004% change from baseline for UX023-CL304 and UX023T-CL201, respectively; p=0.98 for UX023T-CL201).

In a subgroup analysis, the Week 48 results for the six subjects with severe osteomalacia in the TIO Biopsy Analysis Set were more similar to the XLH population in UX023-CL304, including a positive effect on OS/BS (-11.0%; p=0.248). It is also noted that osteomalacia seems have been more pronounced in Study UX023-CL304 based on baseline OS/BS and O.Th. As there was a trend towards a better effect on OS/BS in the post hoc analysis in subjects with severe osteomalacia at baseline in UX023T-CL201, the difference in treatment effect on OS/BS between the studies could in part be explained by a difference in the degree of baseline osteomalacia

Mineralisation lag time (Mlt) was readable at both baseline and Week 48 for only three subjects in UX023T-CL201. For the remaining eight subjects, Mlt data was imputed. No conclusions are considered possible.

Bone biopsy data from study KRN23-002 is considered less robust as data is available for three subjects only and there was large variation in baseline data.

Fracture data

An increasing proportion of healed/partially healed fractures/pseudofractures was seen with time with bone scan in both studies. This could however reflect the natural course of a fracture. As there is no comparator group, no conclusions could be drawn on whether burosumab shortens the time of fracture healing.

As detailed under Methods above, the MAH has undertaken a re-read of fracture data. The number of fractures is low, resulting in small and sometimes contradictory results when comparing the effect of burosumab on single fracture locations between the studies and between the modalities. Notwithstanding, there was, as in the original reads, a consistent decrease in the total number of fractures and pseudofractures after initiation of burosumab in both studies and with both modalities also in the re-read A reduction in both the number of patients reporting symptomatic fractures as adverse events and in the number of fractures reported in UX023T-CL201 was seen after initiation of burosumab treatment. Taken together, numerically, from the blinded re-reads, there seems to be a decrease in fractures with initiation of burosumab treatment offering a support to the proposed indication.

Mobility data

Mobility was evaluated by the sit-to stand test STS) and 6-minute walking test (6MWT) which were secondary endpoints in both TIO studies. In 6MWT the mean (SD) walking distance increased from 309 (210) m at baseline to 331 (175) m (p=0.12) in UX023T-CL201 and from 296 (96) to 354 (116) in KRN23-002. No formal statistical analysis for 6MWT and STS was done in KRN23-002.

For STS the number of repetitions increased from 6.7 (4.0) to 7.7 (4.5) (p= 0.0012) in UX023T-CL201 and from 9.9 (4.5) to 14.1 (4.0) in KRN23-002.

Taken together, the mobility data offers some support to the proposed indication.

Patient-reported Outcomes

In Study UX023T-CL201, numerical reductions were observed over time with burosumab treatment across all Brief pain inventory (BPI) domains. At Week 48, LS mean reductions of -0.9, -0.85 and -1.04 points on a scale from 0-10 were seen for Worst pain, Pain severity and Pain interference, respectively. The improvements did not reach the conservatively estimated level for clinical relevance at the group

level of approximately 1.4 for each of these BPI scales. The results were similar to the corresponding reductions seen in the burosumab arm of the adult XLH study UX023-CL303 (-1.3 for Worst pain and -1 for Pain interference; Pain severity not calculated). Baseline BPI parameters were higher in the XLH compared to the TIO study.

Numerical reductions were observed over time with burosumab treatment also across all Brief fatigue inventory (BFI) domains. At Week 48, LS mean reductions of -0.84, -1.31, -1.85 and -1.64 were seen for Worst fatigue, Fatigue severity, Fatigue interference and Global fatigue, respectively. The improvement in Global fatigue was numerically larger in UX023T-CL201 compared to UX023-CL303 (-1.64 and -0.5, respectively), with similar baseline values. A change score of approximately 1.5 was considered as meaningful at the group level for each of the BFI scores, indicting a stronger treatment effect on BFI versus BPI.

Decreases in pain and fatigue domains also were observed in Study KRN23-002, except for pain interference; however, in this study, the results are more inconsistent, possibly due to large inter-individual variations.

In both studies, increases from baseline in mean scores were noted across all physical health domains of the SF-36v2 instrument, predominantly in the physical domains. No meaningful effect was seen in Mental health in any of the studies or Mental component score in UX023T-CL201 (not calculated for KRN23-002). The SF-36v2 instrument was not used in UX023-CL303.

In summary, there was a general trend towards an improvement of patent reported outcomes, in particular in the BFI score and in the Physical health domains of SF-36v2. Notwithstanding, patient-reported symptoms are considered to be of limited value in open label studies. Furthermore, the subjects had been off conventional treatment with active Vitamin D and/or oral phosphate for several weeks at baseline. This may have worsened physical performance and thereby the reported HRQL at baseline, which in turn may raise expectations of resumed treatment. The patient-reported outcomes, albeit in support for the proposed indication, needs to be interpreted with caution.

Of note, from exit interviews in the studies and from post-marketing experience, testimonies of improvements on Quality of life have emerged. These are to consider as case reports; however, could be considered additional support for a subjective and clinically relevant benefit of burosumab in at least some subjects with TIO.

Assessment of paediatric data on clinical efficacy

There is a Paediatric Investigation Plan waiver in place that was granted on the grounds that significant therapeutic benefit cannot be demonstrated in the paediatric population due to the lack of feasibility of conducting paediatric trials due to the extreme rarity of the TIO condition in paediatrics. However, rare cases of non-resectable tumours do exist also in the paediatric population. The MAH therefore proposes to include children above the age of 1 year in the indication. In this context, it is noted that burosumab is already authorised in this indication in the US from in patients aged from 2 years.
The MAH has clarified that the US indication for treatment in the TIO population from two years of age as opposed to the indication from the age of one year sought in Europe is due to a request from the FDA due to a lack of data in children under the age of three. Finally, the MAH comments that there are extensive safety data available from the XLH population from 1 year and cite this as support of safety in this age cohort while acknowledging the differing pathologies of XLH and TIO. This argumentation is accepted.

Burosumab is indicated in children with XLH from the age of one year. Given the mechanistic relationship with XLH, the safety profile from children and adolescents with XLH is considered possible to extrapolate

to the paediatric TIO population. There are also no indications from the very limited safety data base, that any specific safety issues should apply to the adult TIO population compared to the XLH population.

The dosing regimen for this paediatric population is discussed under subheading "dosing" above.

2.4.3. Summary of clinical efficacy

In total, not more than 27 subjects were enrolled in the two studies in the application to extend the indication for Crysvita to include treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised, in patients aged 1 year and over. It is reasonable to assume that the PK/PD of burosumab would be similar in paediatric patients to that in adult patients with TIO, and that any potential differences in the PD relationship between adults and paediatrics is likely to be captured by the proposed weight-based posology of burosumab.

The negative consequences of longstanding hypophosphataemia on skeletal health and quality of life are well known. TIO associated hypophosphatemia results in many structural and metabolic consequences that contribute to a complex array of symptoms, especially stiffness and pain, as well as poor mineralisation with subsequent fractures/pseudofractures which together cause a decrease in physical function and mobility, leading to substantially impaired overall health.

In total, 50% of the subjects in UX023T-CL201 and 69% in KRN023-002 reached the endpoint of achieving mean serum phosphorus levels above the lower limit of normal at the mid-point of the dose interval. The two TIO-studies also showed an increase in serum phosphate compared to the baseline level which was sustained throughout the study. This increase is considered to be of clinical relevance and could be considered a support for the applied indication. Numerical improvement of bone mineralisation was seen both on bone biopsies and biochemical markers of bone remodelling. The number of new fractures/pseudofractures decreased over time in Study UX023T-CL201. This is also considered clinically relevant and may be seen as support for a new indication Furthermore, the mobility data as assessed by the 6-minute walking test and the sit-to-stand test offers some support to the proposed indication.

On the other hand, there are several limitations in study design and study conduct. Such limitations include lack of a prospective discussion on a minimum required level of efficacy for the study to be interpreted as successful and absence of a suitable control arm, and study UX023T-CL201 analyses were conducted without any consideration concerning multiplicity. PRO data are considered less robust in an open label setting and for some analyses, data from very few subjects was available and the magnitude of improvement is partly modest.

With this said, the difficulties to conduct scientific studies in an ultra-rare disease as TIO, with approximately 500 known cases worldwide, are acknowledged. Differences in disease severity and duration, levels of FGF-23, dosing and compliance with oral phosphate/active vitamin D treatment prior to study entry are additional obstacles which likely have contributed to the complexity of the study results. In this context, the positive trends and numerical improvements in fracture data, bone mineralisation and Quality of life, albeit not fully robust, could be considered supportive of a beneficial effect of burosumab on subjects with TIO associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised. The clinical benefit is further supported by case reports from the literature and individual testimonies from study subjects reporting considerable improvements in signs and symptoms of TIO since beginning treatment with burosumab.

In addition, although the underlying causes of TIO, and XLH are unique, both conditions are characterised by elevated FGF23, resulting in excessive renal phosphate wasting by impaired phosphate reabsorption, reduced vitamin D synthesis, and chronic hypophosphataemia. Effects of similar magnitude on serum

phosphate with burosumab treatment have been reported for both conditions, taking a more conservative starting dosing in the TIO study population into consideration. There are no indications that normalisation of serum phosphate would not lead to similar beneficial effect on e.g. bone mineralisation and quality of life in the TIO population as in the XLH population. The same limitations apply for TIO subjects with longstanding hypophosphataemia as for XLH subjects started on burosumab in adult age. In the light of the same and very specific pathogenetic mechanism in both conditions, extrapolation of efficacy results from the XLH studies in combination with the (less robust) results from the TIO study, is considered to support to the extended indication to *FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised, in children and adolescents aged 1 to 17 years and in adults*".

2.4.4. Conclusions on the clinical efficacy

The CHMP considers that, despite the well-recognised study limitations and the small data set, the totality of evidence is sufficient to support an extension of indication for Crysvita to include the treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in in children and adolescents aged 1 to 17 years and in adults.

2.5. Clinical safety

Introduction

The adult safety database for the approved indication XLH 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.

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 the open label placebo-controlled study 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%).

In the adult XLH 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 "investigations" (21% vs 14%). 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.

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).

Patient exposure

Patient exposure to burosumab in the TIO population is summarised in Table 33.

Table 33: Exposure to Burosumab in Studies UX023T-CL201 and KRN23-002

Parameter Statistics	UX023T-CL201 (N = 14)	KRN23-002 (N = 13)	Total (N = 27)
Cumulative exposure (subject-years)	36.12	26.67	62.79
Duration of exposure (weeks)			
Mean (SD)	134.62 (49.154)	107.05 (27.785)	121.35 (41.969)
Median (Min, Max)	149.71 (24.0, 197.0)	115.86 (15.7, 116.3)	116.14 (15.7, 197.0)
Duration of exposure category (n [%])			
≥1 day to <12 weeks	0	0	0
≥12 to <24 weeks	0	1 (7.69)	1 (3.70)
≥24 to <48 weeks	1 (7.14)	0	1 (3.70)
≥48 to <72 weeks	1 (7.14)	0	1 (3.70)
≥72 to <96 weeks	1 (7.14)	0	1 (3.70)
≥96 to <120 weeks	0	12 (92.31)	12 (44.4)
≥120 to <144 weeks	2 (14.69)	0	2 (7.41)
≥144 weeks	9 (64.29)	0	9 (33.33)
Total dose (mg/kg)			
Mean (SD)	23.63 (17.844)	22.82 (15.337)	23.24 (16.369)
Median (Min, Max)	19.90 (0.8, 67.5)	20.00 (2.7, 48.5)	20.00 (0.8, 67.5)
Average dose per 4-week period (mg/kg)			
Mean (SD)	0.7 (0.446)	0.84 (0.485)	0.77 (0.462)
Median (Min, Max)	0.64 (0.0, 1.8)	0.70 (0.1, 1.7)	0.70 (0.0, 1.8)
Number of doses per subject			
Mean (SD)	31.64 (13.976)	26.46 (6.948)	29.15 (11.265)
Median (Min, Max)	36.00 (4.0, 49.0)	29.00 (4.0, 29.0)	29.00 (4.0, 49.0)

Max = maximum; Min = minimum; N = total number of subjects in analysis set; SD = standard deviation.

Adverse events

A summary of treatment-emergent adverse events in both studies is presented in Table 34.

Table 34: Summary of Treatment-Emergent Adverse Events in Studies UX023T-CL201 and KRN23-002

Category	UX023T-CL201 (N = 14) n (%)	KRN23-002 (N = 13) n (%)	Total (N = 27) n (%)
Subjects with TEAEs	14 (100)	12 (92.3)	26 (96.3)
Maximum severity			
Grade 5	1 (7.1)	0	1 (3.7)
Grade 4	0	2 (15.4)	2 (7.4)
Grade 3	6 (42.9)	2 (15.4)	8 (29.6)
Grade 2	6 (42.9)	8 (61.5)	14 (51.9)
Grade 1	1 (7.1)	0	1 (3.7)
Related TEAEs	9 (64.3)	5 (38.5)	14 (51.9)
Serious TEAEs [a]	7 (50.0)	4 (30.8)	11 (40.7)
Related Serious TEAEs [a]	0	0	0
Grade 3 or 4 TEAEs	7 (50.0)	4 (30.8)	11 (40.7)
TEAEs Leading to Study Discontinuation	0	0	0
TEAEs Leading to Death	1 (7.1)	0	1 (3.7)
TEAEs of Interest			
Injection site reaction [b]	3 (21.4)	1 (7.7)	4 (14.8)
Hypersensitivity [c]	2 (14.3)	4 (30.8)	6 (22.2)
Hyperphosphataemia [d]	2 (14.3)	0	2 (7.4)
Ectopic mineralisation [e]	3 (21.4)	0	3 (11.1)
Restless legs syndrome [f]	2 (14.3)	0	2 (7.4)

MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in analysis set; n = number of subjects with at least one specified event; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event.

a: This table only includes SAEs up to 11 Jan 2019 for Study UX023T-CL201 and up to the Week 112 visit for Study KRN23-002.

b: Defined by MedDRA High-Level Term Injection site reaction.

c: Defined by MedDRA narrow SMQ Hypersensitivity.

d: Includes the MedDRA Preferred Terms Hyperphosphataemia, Blood phosphate increased, Blood phosphate abnormal.

e: Defined using a MedDRA search of "calcification".

Most frequently reported Adverse events

The most common TEAEs reported (≥ 20% of subjects) included nasopharyngitis (44.4%), arthralgia (37.0%), pain in extremity (37.0%), upper respiratory tract infection (25.9%), and cough (22.2%). A summary of TEAE per SOC is given in Table 35.

Table 35: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in Descending Frequency (All System Organ Classes; Preferred Terms with ⩾3 Subjects Overall) in Studies UX023T-CL201 and KRN23-002

System Organ Class Preferred Term	UX023T-CL201 (N = 14) n (%)	KRN23-002 (N = 13) n (%)	Total (N = 27) n (%)
Subjects with any TEAE	14 (100)	12 (92.3)	26 (96.3)
Infections and Infestations	13 (92.9)	10 (76.9)	23 (85.2)
Nasopharyngitis	4 (28.6)	8 (61.5)	12 (44.4)
Upper respiratory tract infection	7 (50.0)	0	7 (25.9)
Urinary tract infection	4 (28.6)	0	4 (14.8)
Bronchitis	3 (21.4)	0	3 (11.1)
Influenza	2 (14.3)	1 (7.7)	3 (11.1)
Septic shock	1 (7.1)	2 (15.4)	3 (11.1)
Musculoskeletal and Connective Tissue Disorders	14 (100)	8 (61.5)	22 (81.5)
Arthralgia	8 (57.1)	2 (15.4)	10 (37.0)
Pain in extremity	9 (64.3)	1 (7.7)	10 (37.0)
Back pain	4 (28.6)	1 (7.7)	5 (18.5)
Muscle spasms	4 (28.6)	1 (7.7)	5 (18.5)
Myalgia	3 (21.4)	2 (15.4)	5 (18.5)
Musculoskeletal pain	3 (21.4)	0	3 (11.1)
Gastrointestinal Disorders	10 (71.4)	8 (61.5)	18 (66.7)
Diarrhoea	4 (28.6)	1 (7.7)	5 (18.5)
Nausea	3 (21.4)	2 (15.4)	5 (18.5)
Constipation	2 (14.3)	2 (15.4)	4 (14.8)
Vomiting	3 (21.4)	1 (7.7)	4 (14.8)
Large intestine polyp	1 (7.1)	2 (15.4)	3 (11.1)
Toothache	2 (14.3)	1 (7.7)	3 (11.1)
Injury, Poisoning, and Procedural Complications	11 (78.6)	6 (46.2)	17 (63.0)
Contusion	2 (14.3)	3 (23.1)	5 (18.5)
Fall	4 (28.6)	0	4 (14.8)
Tooth fracture	2 (14.3)	2 (15.4)	4 (14.8)
Procedural pain	3 (21.4)	0	3 (11.1)
General Disorders and Administration Site Conditions	9 (64.3)	4 (30.8)	13 (48.1)
Fatigue	2 (14.3)	3 (23.1)	5 (18.5)
Injection site reaction	2 (14.3)	1 (7.7)	3 (11.1)
Pain	3 (21.4)	0	3 (11.1)
Nervous System Disorders	6 (42.9)	6 (46.2)	12 (44.4)
Dizziness	2 (14.3)	2 (15.4)	4 (14.8)
Headache	0	3 (23.1)	3 (11.1)
Respiratory, Thoracic, and Mediastinal Disorders	10 (71.4)	2 (15.4)	12 (44.4)
Cough	6 (42.9)	0	6 (22.2)
Nasal congestion	3 (21.4)	0	3 (11.1)
Respiratory tract congestion	3 (21.4)	0	3 (11.1)
Investigations	8 (57.1)	2 (15.4)	10 (37.0)
Amylase increased	3 (21.4)	0	3 (11.1)
Neoplasms Benign, Malignant, And Unspecified (Incl Cysts and Polyps)	9 (64.3)	1 (7.7)	10 (37.0)
Neoplasm progression	5 (35.7)	0	5 (18.5)
Metabolism and Nutrition Disorders	7 (50.0)	1 (7.7)	8 (29.6)
Renal and Urinary Disorders	5 (35.7)	3 (23.1)	8 (29.6)
Skin and Subcutaneous Tissue Disorders	4 (28.6)	4 (30.8)	8 (29.6)
Eczema	0	3 (23.1)	3 (11.1)
Rash	1 (7.1)	2 (15.4)	3 (11.1)
Psychiatric Disorders	4 (28.6)	2 (15.4)	6 (22.2)
Depression	2 (14.3)	1 (7.7)	3 (11.1)
Vascular Disorders	3 (21.4)	2 (15.4)	5 (18.5)
Hypertension	2 (14.3)	1 (7.7)	3 (11.1)
Eye Disorders	1 (7.1)	3 (23.1)	4 (14.8)
Hepatobiliary Disorders	2 (14.3)	2 (15.4)	4 (14.8)
Ear and Labyrinth Disorders	2 (14.3)	1 (7.7)	3 (11.1)
Blood and Lymphatic Disorders	1 (7.1)	1 (7.7)	2 (7.4)
Cardiac Disorders	2 (14.3)	0	2 (7.4)
Reproductive System and Breast Disorders	2 (14.3)	0	2 (7.4)
Immune System Disorders	0	1 (7.7)	1 (3.7)

Adverse Events Related to Treatment

In total, 14 subjects (51.9%) had TEAEs that were assessed as related to burosumab by the investigator. The majority of related TEAEs were only reported in one subject across both studies. Related TEAEs that

were reported for at least two subjects across studies included injection site reaction, hyperphosphataemia, vitamin D deficiency and rash.

Serious adverse event/deaths/other significant events

Fatal events

One (7.1%) death due to cardiac arrest was reported in Study UX023T-CL201 at the Week 144 data cut-off. This event was assessed by the investigator and Sponsor as unrelated to study drug.

After the Week 144 data cut-off, another subject in Study UX023T-CL201 died from events of ovarian cancer and multi-organ failure, which were considered by the investigator and Sponsor as unrelated to burosumab.

Serious adverse events

Serious TEAEs were reported for seven subjects (50%) in Study UX023T-CL201, and four subjects (30.8%) in Study KRN23-002 (Table 36), none were assessed by the investigator and Sponsor as related to burosumab treatment.

Table 36: List of Subjects with Serious Adverse Events in Studies UX023T-CL201 and KRN23-002

Subject No.	Preferred Term	Severity	Relationship to Study Drug	Outcome
			Study UX023T-CL201	
138-105	Neoplasm progression	Grade 3	Not related	Recovered/Resolved with sequelae
156-103	Tumour compression	Grade 3	Not related	Recovered/Resolved
	Acute respiratory failure	Grade 4	Not related	Recovered/Resolved
	Pickwickian syndrome	Grade 3	Not related	Recovered/Resolved
	Cholangitis	Grade 3	Not related	Recovered/Resolved
	Pancreatitis	Grade 3	Not related	Recovered/Resolved
	Septic shock	Grade 3	Not related	Recovered/Resolved
	Cardiac arrest	Grade 5	Not related	Death
163-101	Neoplasm progression	Grade 3	Unlikely	Not recovered
175-101	Neoplasm progression	Grade 2	Not related	Recovered/Resolved
175-102	Metastases to lung	Grade 3	Not related	Recovered/Resolved
	Thyroid mass	Unknown[a]	Not related	Recovered/Resolved
175-103	Pleural effusion	Grade 2	Not related	Not recovered
	Multi-organ failure[b]	Grade 5	Not related	Death
	Pleural effusion[b]	Grade 3	Not related	Not recovered
	Pulmonary embolism[b]	Grade 4	Not related	Not recovered
	Ascites[b]	Grade 2	Unlikely	Not recovered
	Ovarian cancer stage IV[b]	Grade 5	Not related	Death
175-104	Neoplasm progression	Grade 3	Not related	Recovered/Resolved
	Neoplasm progression	Grade 3	Not related	Not recovered
	Hypophosphataemia[b]	Grade 3	Not related	Recovered/Resolved
	Acute kidney injury[b]	Grade 2	Not related	Not recovered
193-101	Tooth abscess	Grade 3	Not related	Recovered/Resolved
	Sialoadenitis	Grade 3	Not related	Recovered/Resolved
	Rheumatoid arthritis	Grade 3	Not related	Recovered/Resolved
			Study KRN23-002	
101-02	Infectious gastroenteritis	Grade 4	Not related	Recovered/Resolved
	Septic shock	Grade 4	Not related	Recovered/Resolved
	Large intestine polyp	Grade 3	Not related	Recovered/Resolved
102-01	Depression aggravated[b]	Unknown[a]	Not related	Not recovered
102-02	Large intestine polyp	Grade 3	Not related	Recovered/Resolved
	Gouty arthritis[b]	Unknown[a]	Not related	Recovered/Resolved
102-03	Herpes zoster	Grade 3	Not related	Recovered/Resolved
201-01	Septic shock	Grade 4	Not related	Recovered/Resolved
202-02	Meningioma[b]	Unknown[a]	Not related	Not recovered

The data cut-off date for SAEs reported in this document as narratives is 18 Aug 2020.
a: Event grades were not provided.
b: Event occurred after the Week 144 (Study UX023T-CL201) or Week 112 (Study KRN23-002) data cut-off.

Selected narratives are briefly summarised below.

Prespecified Events to Monitor

Adverse events in five prespecified areas to monitor for burosumab are summarised in Table 37 and briefly discussed below.

Table 37: Overall Summary of Predefined Treatment-Emergent Adverse Events Monitored in Studies UX023T-CL201 and KRN23-002

	UX023T-CL201 (N = 14) n (%)		KRN23-002 (N = 13) n (%)		Total (N = 27) n (%)	
	Events	Subjects	Events	Subjects	Events	Subjects
Prespecified Event to Monitor	n	n (%)	n	n (%)	n	n (%)
Injection site reactions	8	3 (21.4)	1	1 (7.7)	9	4 (14.8)
Hypersensitivity	4	2 (14.3)	10	4 (30.8)	14	6 (22.2)
Hyperphosphataemia	2	2 (14.3)	0	0	2	2 (7.4)
Ectopic mineralisation	3	3 (21.4)	0	0	3	3 (11.1)
Restless legs syndrome	3	2 (14.3)	0	0	3	2 (7.4)

The total exposure-adjusted event incidence of Injection site reactions was 0.82 events/year across both studies compared to 0.80 events/year in the adult XLH studies.

The total exposure-adjusted event incidence of Hypersensitivity was 1.206 events/year across both studies. Six subjects (22%) reported at least one hypersensitivity reaction (Eczema [3], Rash [3], Application site rash [1], Drug eruption [1], hypersensitivity [1]). The event of application site rash in Study UX023T-CL201 was considered related to topical antimicrobial wash by Investigator. There were no serious hypersensitivity TEAEs in any subject. Across all repeat-dose adult XLH studies, 55 hypersensitivity TEAEs were reported for 33 (18.8%) subjects.

There were two Hyperphosphataemia events reported for two subjects (14.3%) in Study UX023T-CL201 and no hyperphosphataemia events reported in Study KRN23-002, with a total exposure-adjusted event incidence of 0.417 events/year across both studies affecting 7.4% of the TIO population. In the adult XLH population, eight subjects (4.5%) reported hyperphosphataemia.

- *One subject* had one event of hyperphosphataemia (serum phosphate: 5.9 mg/dL; 1.9 mmol/L) on Study Day 16. Of note, the subject received 0.3 mg/kg of burosumab at baseline when the subject's serum phosphate level was within the normal range (3.0 mg/dL).
- *Once subject* received radiation therapy over a 5-week period, commencing approximately at Week 36. The subject developed hyperphosphataemia at approximately Week 68, which was thought to be the result of decreased tumour burden and lower FGF23 levels following radiation. Treatment was resumed at Week 76 at a lower dose. The subject had no further incidences of hyperphosphataemia.

There were three Ectopic mineralisation events reported for three subjects. The total exposure-adjusted event incidence was 0.438 events/year. Of the three subjects, the events were confounded in two subjects. One of these subjects, who experienced calculus bladder, had a previous history of kidney stones, and one subject, who experienced nephrolithiasis, presented with non-obstructive nephrolithiasis on CT at baseline.

Renal ultrasounds were used to assess shifts in nephrocalcinosis and nephrolithiasis. All subjects in Study UX023T-CL201 and nine subjects (69.2%) in Study KRN23-003 entered the studies with a baseline nephrocalcinosis score of 0 (Table 38).

Table 38: Shifts in Renal Ultrasound Nephrocalcinosis Scale in Studies UX023T-CL201 and KRN23-002

Baseline Score	Baseline Scores UX023T-CL201 (N=14) KRN23-002 (N=13) Total (N=27) n (%)	Max Post-Baseline Score			
		0	1	2	3
0	UX023T-CL201: 14 (100)	12 (85.7)	2 (14.3)	0	0
	KRN23-002: 9 (69.2)	9 (69.2)	0	0	0
	Total: 23 (85.2)	21 (77.8)	2 (7.4)	0	0
1	UX023T-CL201: 0	0	0	0	0
	KRN23-002: 3 (23.1)	0	3 (23.1)	0	0
	Total: 3 (11.1)	0	3 (11.1)	0	0
2	UX023T-CL201: 0	0	0	0	0
	KRN23-002: 1 (7.7)	0	0	0	1 (7.7)
	Total: 1 (3.7)	0	0	0	1 (3.7)

N = total number of subjects in analysis set; n = number of subjects with specified score.
Shaded cells indicate no change from baseline.

In the pivotal adult XLH study UX023-CL303, 16% of the subjects in the burosumab arm and 18% of the subjects in the placebo arm reported a shift +1 Grade in nephrocalcinosis.

All but one subject across both studies entered the study without nephrolithiasis (Table 39).

Table 39: Shifts in Renal Ultrasound Nephrolithiasis in Studies UX023T-CL201 and KRN23-002

Baseline Presence/Absence	Baseline UX023T-CL201 (N=14) KRN23-002 (N=13) Total (N=27) n (%)	Max Post-Baseline	
		No	Yes
No	UX023T-CL201: 13 (92.9)	12 (85.7)	1 (7.1)
	KRN23-002: 13 (100)	12 (92.3)	1 (7.7)
	Total: 26 (96.3)	24 (88.9)	2 (7.4)
Yes	UX023T-CL201: 1 (7.1)	0	1 (7.1)
	KRN23-002: 0	0	0
	Total: 1 (3.7)	0	1 (3.7)

N = total number of subjects in analysis set; n = number of subjects with specified score.
Shaded cells indicate no change from baseline.

In the adult XLH study, overall, there was no apparent difference between the treatment groups in nephrolithiasis findings by renal ultrasound.

There were three Restless legs (RLS) events (two events of RLS and one event of sensory disturbance) reported for two subjects (14.3%) in Study UX023T-CL201 and no RLS events reported in Study KRN23-002, with a total exposure-adjusted event incidence of 0.769 events/year across both studies. RLS was reported in 24 (13.6%) subjects in repeat-dose adult XLH studies.

Other Adverse events of interest

Renal Safety

A renal safety analysis was conducted to address concerns for potential antibody-dependent cellular cytotoxicity and its potential impact on kidneys in the context of elevated serum FGF23 concentrations with burosumab treatment.

There was one event of acute kidney injury in each study; both events were severe (Grade 3), assessed by the investigator as unrelated to burosumab, and resolved. One subject with a history of hypertension, hypercalcemia, and kidney stones, experienced creatinine renal clearance decrease and renal impairment,

both of which were mild (Grade 1), assessed by the investigator as unrelated to burosumab, and were resolving and resolved, respectively. One subject experienced blood creatinine increase, which was mild (Grade 1) and not resolved as of the data cut-off date, assessed by the investigator as unrelated to burosumab.

Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)

A total of nine subjects (64.3%) in Study UX023T-CL201 had 20 TEAEs that were classified under the MedDRA SOC "Neoplasms benign, malignant and unspecified (including cysts and polyps)." (Table 40) Seven events were serious TEAEs occurring in six subjects. None of the events were considered related to burosumab by the investigator.

Table 40: Summary of TEAEs Under MedDRA SOC "Neoplasms benign, malignant and unspecified (including cysts and polyps)" (TIO Analysis Set UX023T-CL201)

System Organ Class Preferred Term	Total Subjects (N = 14) n (%)	Total Events n	Subject ID	Related to PMT?
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (64.3)	20		
Neoplasm progression	5 (35.7)	8	138-105, 156-102, 163-101, 175-101, 175-104	Yes
Metastases to lung	1 (7.1)	1	175-102	Yes
Metastases to pancreas	1 (7.1)	1	175-104	Yes
Pancreatic carcinoma metastatic [a]	1 (7.1)	1	175-104	Yes
Tumour compression	1 (7.1)	1	156-103	Yes
Basal cell carcinoma	1 (7.1)	3	176-101	No
Neuroma	1 (7.1)	1	156-102	No
Squamous cell carcinoma	2 (14.3)	2	176-101, 193-102	No
Thyroid neoplasm	1 (7.1)	1	175-102	No

PMT = phosphaturic mesenchymal tumor

[a] The verbatim term of this event was "Worsening Para Pancreatic and Pancreatic Tail Mestastases," which mapped to the Preferred Term (PT) of Pancreatic Carcinoma Metastatic. However, this subject had a PMT metastases to the pancreas, and did not have primary pancreatic carcinoma that metastasized, as the PT might indicate.

In Study KRN23-002, one subject (7.7%) had one nonserious TEAE of skin papilloma (Grade 2/moderate severity) reported under the MedDRA SOC 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)'. This event was considered by the investigator as unrelated to treatment with burosumab (no action taken with the study drug), and was resolving as of the data cut-off date.

Adverse Drug Reactions Section of the Proposed Labelling

Criteria used for defining ADRs included the frequency of the TEAE (≥10% or ≥3 subjects) in the pooled data for Study UX023T-CL201 up to Week 144 and Study KRN23-002 up to Week 112. Pooled TEAEs occurring in < 10% of subjects and < 3 subjects were also reviewed for potentially important ADRs.

There were no new ADRs identified in the TIO population that are not already ADRs in either the adult or paediatric XLH population.

The adverse drug reactions proposed to be amended to section 4.8 as a separate table for the TIO population are summarised below (Table 41).

Table 41: Proposed Adverse Drug Reactions in TIO

Preferred Term	Overall Subject Incidence (N = 27) n (%)
Tooth abscess [a]	5 (19)
Muscle spasms	5 (19)
Dizziness	4 (15)
Constipation	4 (15)
Injection site reaction [b]	4 (15)
Rash [c]	4 (15)
Headache	3 (11)
Vitamin D deficiency	2 (7)
Hyperphosphataemia [d]	2 (7)
Restless legs syndrome	2 (7)

a: Tooth abscess is defined PTs "Tooth abscess" and "Tooth ache".
b: Injection Site Reactions is defined by PTs "Injection Site Reaction", "Injection Site Pain" and "Injection Site Swelling".
c: Rash is defined by PTs "Rash" and "Rash papular".
d: Hyperphosphataemia is defined by PTs "Blood phosphate increased" and "Hyperphosphataemia".

Laboratory findings

Serum Intact Parathyroid Hormone (iPTH)

Most subjects entered the studies with high iPTH levels at baseline. On average, these values decreased to closer to the reference range of iPTH. There were no TEAEs related to iPTH levels.

Serum Calcium

There was an overall mean increase of 0.76 and 0.72 mg/dL at Weeks 120 and 132, respectively, in Study UX023T-CL201 with a maximum value of 12.1 mg/dL at both timepoints. These increases were largely driven by a subject with tertiary hyperparathyroidism and a subject with hypoparathyroidism managed by calcium supplements.

One subject with ongoing history of hypercalcemia and tertiary hyperparathyroidism had 3 TEAEs of hypercalcemia, which were considered unrelated to burosumab treatment by the investigator). Another subject with a history of hypocalcaemia had a TEAE of blood calcium increased of moderate (Grade 2) severity, which was considered unrelated to burosumab by the investigator.

Serum Vitamin D

Levels of 1,25-dihydroxyvitamin D (1,25 (OH)2D) generally increased above baseline during both studies as expected with burosumab treatment (Table 25). Levels of 25-hydroxyvitamin D (25 OHD) overall increased slightly in Study UX023T-CL201 and decreased slightly in Study KRN23-002.

Serum Amylase

All but one subject entered the studies with a baseline serum amylase Grade 0. Of these subjects, one subject shifted to Grade 1, 2 subjects to Grade 2, and 1 subject to Grade 4 at maximum Grade post-baseline. One subject entered Study UX023T-CL201 at a baseline Grade 2 and had a maximum post-baseline shift to Grade 3.

Three subjects in Study UX023T-CL201 had TEAEs of amylase increased, all of which were mild (Grade 1) in severity and were determined by the investigator as unrelated to burosumab. One TEAE of amylase increased occurred in the context of the serious TEAE of pancreatitis.

Other Serum Chemistry

Bicarbonate levels generally increased slightly in Study KRN23-002 (but remained within the normal range) but showed no overall change in Study UX023T-CL201. There were no consistent or clinically meaningful changes in any other serum chemistry parameter.

Serum Creatinine

There were no clinically meaningful changes over time in mean serum creatinine concentrations in either study.

One subject in Study UX023T-CL201 had 3 TEAEs related to creatinine metabolism: increased creatinine, decreased creatinine clearance, and elevated creatinine. All of the events were mild (Grade 1) and determined by the investigator to be unrelated to burosumab. Another subject in Study UX023T-CL201 had a TEAE of elevated creatinine, which was mild (Grade 1) in severity and determined by the investigator to be unrelated to burosumab.

Haematology

No clinically meaningful changes in haematology parameters were observed in either study.

There was one TEAE of leukocytosis in Study UX023T-CL201, which was mild (Grade 1) in severity and determined by the investigator to be unrelated to burosumab.

Vital signs

Blood pressure

No clinically meaningful changes in vital signs were noted during either study.

There was one TEAE of systolic blood pressure increase in Study UX023T-CL201, which was mild in severity and determined by the investigator to be unrelated to burosumab. There were three events of hypertension in two subjects in Study UX023T-CL201, all were determined by the investigator to be unrelated to burosumab. Subject 156-103 had one mild (Grade 1) and one moderate (Grade 2) event, both resolved. Subject 193-101 had a mild (Grade 1) event, which was not resolved as of the data cut-off. There was one event of hypertension in Study KRN23-002, which was moderate (Grade 2), determined by the investigator to be unrelated to burosumab.

Electrocardiograms

Overall, no clinically meaningful changes in electrocardiogram (ECG) parameters were noted in either study.

Shifts in ECG corrected QT interval Fridericia are summarised in table 42

Table 42: Shifts in Electrocardiogram QTcF Interval in Studies UX023T-CL201 and KRN23-002

Baseline Category	Baseline UX023T-CL201 (N=14) KRN23-002 (N=13) Total (N=27) n (%)	Max Post-Baseline Category			
		≤450 ms	>450 - ≤480 ms	>480 - ≤500 ms	>500 ms
≤450 ms	UX023T-CL201: 13 (92.9)	11 (78.6)	2 (14.3)	0	0
	KRN23-002: 10 (76.9)	8 (61.5)	2 (15.4)	0	0
	Total: 23 (85.2)	19 (70.4)	4 (14.8)	0	0
>450 - ≤480 ms	UX023T-CL201: 0	0	0	0	0
	KRN23-002: 2 (15.4)	1 (7.7)	1 (7.7)	0	0
	Total: 2 (7.4)	1 (3.7)	1 (3.7)	0	0
>480 - ≤500 ms	UX023T-CL201: 0	0	0	0	0
	KRN23-002: 1 (7.7)	0	0	1 (7.7)	0
	Total: 1 (3.7)	0	0	1 (3.7)	0
>500 ms	UX023T-CL201: 1 (7.1)	0	1 (7.1)	0	0
	KRN23-002: 0	0	0	0	0
	Total: 1 (3.7)	0	1 (3.7)	0	0

N = total number of subjects in analysis set; n = number of subjects in specified category.
Shaded cells indicate no change from baseline.

Echocardiogram (ECHO)

Two subjects in KRN23-002 had abnormal ECHO findings at baseline.

There was one TEAE of abnormal echocardiogram (mild aortic valve thickening resulting in ectopic mineralisation score) in Study UX023T-CL201, which was mild (Grade 1) in severity and determined by the investigator to be unrelated to burosumab.

In Study UX023T-CL201, ectopic mineralisation was also assessed using ECHO. At Baseline, 8 subjects (57.1%) had ectopic mineralization Grade 0, and 6 subjects (42.9%) had ectopic mineralization Grade 1. Minimal changes in ECHO grades were seen with burosumab treatment over time. At Week 144, 2 subjects shifted from Grade 0 to Grade 1, and 1 subject shifted from Grade 1 to Grade 0.

Anti-drug Antibodies

Across both studies, all subjects tested negative for anti-drug antibodies (ADAs) at baseline. Two subjects (14.3%) in Study UX023T-CL201 were positive for ADAs at Week 120 and were subsequently negative at Week 144. Both subjects tested negative for neutralising antibodies at Week 120. One of these subjects had four ISR TEAEs during the study; however, the ISRs did not coincide with the time point of the positive ADA test. The other subject (193-101) had no ISR or hypersensitivity TEAEs. The remaining 12 subjects (85.7%) tested negative for ADAs at all post-baseline time points tested.

In Study KRN23-002, all subjects tested negative for ADAs at all post-baseline assessments. No subject tested positive for neutralising antibodies in either study.

Safety in special populations

Age: Safety data in subjects > 65 years old (N=9) did not show any meaningful differences from the overall study population.

Sex: Review of safety data by sex revealed no meaningful differences

Race: There were no clinically meaningful differences in safety observed between Study UX023T-CL201, which included a majority of white subjects, and Study KRN23-002, which included all Asian subjects, suggesting no difference in the safety profile between these two groups.

Renal and Hepatic Impairment: Renal impairment can induce abnormal mineral metabolism which may increase phosphate concentrations greater than expected with burosumab alone. This can lead to increased risk of hyperphosphataemia and nephrocalcinosis. Subjects with severe kidney impairment were excluded from Studies UX023T-CL201 and KRN23-002, as they could be prone to increases in serum

phosphate and calcium. Burosumab treatment is also contraindicated in XLH patients with severe renal impairment or end stage renal disease. Renal safety in subjects with XLH is being monitored in a long-term disease monitoring programme, Study UX023-CL401.

Subjects with a history of liver impairment were not excluded from burosumab clinical trials. Medical history at baseline was reviewed, and only 1 subject had a history of acute hepatitis. There were no TEAEs related to hepatic impairment in this subject. Four subjects had TEAEs in the Hepatobiliary Disorders SOC, none of which were considered related to treatment by the investigator.

Paediatric population: Whilst no clinical data exists in paediatric patients with TIO, given the evidence from the use of burosumab in the treatment of adults and children with XLH and the comparable PD effect of blocking excess FGF23 in adults and children, the safety profile and pharmacological effect of burosumab in paediatric patients with TIO would be expected to be comparable to the adult TIO population.

Safety related to drug-drug interactions and other interactions

No drug interaction studies have been conducted with burosumab in subjects with TIO.

Concomitant use of burosumab with oral phosphate and/or active vitamin D analogues is contraindicated as this combination increases phosphate concentrations greater than expected with burosumab alone. This increase may result in hyperphosphataemia which can induce nephrocalcinosis.

Discontinuation due to adverse events

One serious TEAE (neoplasm progression) in Study UX023T-CL201 led to study treatment discontinuation. The event was a Grade 3 and was assessed by the investigator and Sponsor as unrelated to burosumab treatment. Up to the ISS data cut-offs (11 Jan 2020 for Study UX023T-CL201 and Week 112 visit for Study KRN23-002), no other TEAEs had resulted in treatment discontinuation.

Post marketing experience

Burosumab is currently approved in the EU for the treatment of XLH in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults. Burosumab was approved in the United States on 17 Apr 2018 for the treatment of XLH in adult and paediatric patients 1 year of age and older; on 27 Sep 2019, the indication was expanded to include infants from 6 months of age. Burosumab is also approved in a number of other countries including Canada (05 Dec 2018; with expansion of the indication in June 2020 to include infants from 6 months of age), Israel (05 Feb 2019) and the United Arab Emirates (12 Feb 2019), for the treatment of XLH in adult and paediatric patients 1 year of age and older.

On 18 Jun 2020, burosumab was approved in the United States for the treatment of FGF23-related hypophosphataemia in TIO associated with PMT that cannot be curatively resected or localised in adult and paediatric patients 2 years of age and older. Burosumab was also approved in Japan on 20 Sep 2019 for the treatment of FGF23-related hypophosphataemic rickets and osteomalacia, including TIO. On 17 Sep 2020, Marketing Authorisation was granted in South Korea for the same indication as Japan. Applications for the treatment of TIO are also planned for other countries including Canada, Australia and Israel.

The most recent postmarketing experience of burosumab in XLH is reflected in the Periodic Safety Update Report covering the period to 18 Aug 2020, and reflects a total of 2,852 patients exposed to burosumab through the commercially sold product or in an early access programme EAPs are approved and ongoing in

national territories of the EU, Switzerland, Latin America, Australia and Gulf Cooperation Council countries. Patient Support Programmes are on-going in Canada, Germany and the United States.

Overall, the majority of AEs reported in post-marketing setting are either expected ADRs with burosumab use and/or the underlying conditions being treated. No significant actions related to safety of burosumab were taken or proposed during this reporting period and there were no changes to the important identified or important potential risks.

Table 43: Cumulative Exposure from the EAP and Post-marketing Experience

		Number of Patients Cumulatively Who Received at Least One Dose of Burosumab Until 31 Jul 2019		
Country	**Commercial**	**EAP**	**Adult/TIO* EAP**	**Total**
Australia	0	56	0	56
Austria	0	16	0	16
Canada	45	17	0	62
Czech Republic	0	4	0	4
Denmark	0	0	1	1
Estonia	0	2	0	2
France	0	135	0	135
GCC	0	32	0	32
Germany	205	0	0	205
Greece	0	2	0	2
Israel	40	0	0	40
Italy	42	0	28	70
Japan	225	0	0	225
Latin America	0	62	2	64
Luxembourg	2	0	0	2
Netherlands	18	0	0	18
Norway	9	0	0	9
Portugal	0	9	0	9
Slovakia	4	0	0	4
Spain	0	44	0	44
Sweden	6	0	1	7
Switzerland	0	5	0	5
United Kingdom	188	0	62	250
United States	1, 582	4	4	1,590
Total	**2,366**	**388**	**98**	**2,852**

EAP = Early Access Programme; GCC = Gulf Cooperation Council.
Note: Patients are only counted in this table once, i.e. if a patient receives burosumab from an EAP and then is transferred to commercially available product, the patient is only counted in the Commercial column.
*Refers to both XLH and TIO; adult XLH patients will be included in this column for territories where they are not included in the approved indication (EU).

2.5.1. Discussion on clinical safety

The total safety data base in TIO subject comprises 27 subjects with a total of 63 patient years. However, there are not considered to be any reasons for why the safety data base for burosumab in the treatment of XLH would not be relevant also for the TIO population. No subjects from the paediatric population were included in the studies. The proposed extension of indication for the treatment of TIO includes subjects aged from one year.

Upon request, the MAH has provided an update of the safety data up to the end of both studies. This summary did not indicate a differing safety profile relative to that previously characterised.

Direct comparisons between the adult XLH and TIO populations are hampered by differences both in the study design and in the study populations. For example, the mean age was substantially higher in the two studies in the TIO population compared to the pivotal adult XLH study UX023-CL303 (57 years, 60 years and 41 years, for UX023T-CL201, KRN23-002 and UX023-CL303, respectively). This may indicate that the TIO population has more co-morbidities and is generally frailer than the adult XLH population.

As in the adult XLH safety database, almost all subjects in the TIO safety set reported at least one TEAE.

The most common TEAEs reported (≥ 20% of subjects) included nasopharyngitis (44.4%), arthralgia (37.0%), pain in extremity (37.0%), upper respiratory tract infection (25.9%), and cough (22.2%). The spectrum of TEAE was similar between the adult XLH and TIO populations. One notable difference was seen in SOC Neoplasms, in which 10/27 subjects (37%) reported at least one event. Most events were serious. Furthermore, unike the XLH population, there were three subjects reporting adverse events of septic shock. This is further discussed below.

Fourteen subjects (52%) were reported with at least one TEAE deemed as reated to treatment. Four related TEAEs were reported for more than one subject across the studies. These four events (injection site reaction, hyperphosphataemia, vitamin D deficiency and rash) are labelled as adverese drug reactions for burosumab.

More subjects in the TIO population reported a SAE (41% vs 16% for the XLH population); however, none of the SAE were deemed as related to burosumab treatment.

In total, ten subjects over the two studies reported at least one SAE associated to the SOC neoplasm. The most common PT was Neoplasm progression (n=4). These four subjects, all had a medical history of mesenchymal tumours with progression, recurrence or metastases before initiating burosumab. It is agreed with the MAH that the events of neoplasm progression in these cases are most probably unrelated to study treatment and rather manifestations of the underlying disease. As pointed out by the MAH, based on its mechanism of action, burosumab treatment is intended to address the FGF23-driven pathophysiology of TIO, and is not expected to impact the natural course of the underlying tumour. This is fully agreed.

Two additional subjects reported an SAE with a preferred term (PT) that seemed to indicate a neoplasm unrelated to the underlying disease (Tumour compression, Metastases to lung); however, in both cases the events were related to a pre-existing mesenchymal tumour. In one subject (PT Meningioma), the lesion was identified several years before study start, precluding a causal association to burosumab treatment.

For the remaining three subjects (PT Large Intestine Polyp [2] and disseminated ovarian cancer), the respective neoplasms were diagnosed during the course of the studies. None of these events were deemed as related by the Investigator/sponsor. The MAH argues that Large Intestine Polyp is a common condition among middle-aged healthy subjects. This is acknowledged. The SAE of ovarian cancer was discussed under fatal events.

All cases of neoplasm progression occurred in Study UX023T-CL201 with no reported cases in KRN23-002. The MAH has clarified that all subjects reporting tumour progression had a previous history of tumour recurrence/progression. Any assessment of the potential cause of the apparent discrepancy in tumour progression between the studies is limited by the low numbers of subjects in each study. PMTs are a rare and heterologous set of neoplasms. Variability in the definition of tumour progression is also a potential aspect to take into consideration. Based on the known pharmacology of burosumab, there is no

expectation of a causal role in tumour progression. Based on this argumentation, the MAH considers this discrepancy in tumour progression between the studies as incidental. This is accepted.

No SAE of septic shock was reported in the adult XLH development program versus three in the TIO population 3/27; 11%). This high rate is somewhat surprising. However, there was nothing remarkable in the narratives of the three events (a 59-year-old man with obesity, gallstone pancreatitis and cholangitis; a 72-year-old man with coliform enteritis from suspected food poisoning and a 75-year-old woman with pyelonephritis). As pointed out earlier, the TIO population was older than the XLH population. No further actions are considered warranted.

Prespecified Events to Monitor for burosumab are Injection site reaction, Hypersensitivity, Hyperphosphataemia, Ectopic mineralisation and Restless leg syndrome. The total exposure-adjusted event incidence for the Prespecified Events to Monitor was generally somewhat higher in the TIO populations; however, there were no substantial differences that merits any further actions, except for Hyperphosphataemia.

Two events of hyperphosphataemia were reported: one in a subject with serum phosphate in the normal range before initiating burosumab and one in subject receiving radiation therapy against the underlying tumour.
The first event reflects the definition of the study population, in which only subjects with a serum phosphate level below lower level of normal (<2.5 mg/dL or 0.8 mmol/L). Thus, this subject should not have been included in the study. Overall, it is highly questionable that burosumab should be started in a subject with normal range serum phosphate regardless of indication. In section 4.4 of the approved SmPC it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range for age. This is considered adequate.
The second event shows the need of extra monitoring and dose adjustments in subjects undergoing treatment against the underlying disease. Information on dose modification and increased serum phosphorus monitoring in the case of a patient undergoing treatment for the underlying tumour has been introduced in sections 4.2 and 4.4 of the SmPC.

In general, there were large variations in laboratory values both between and within the studies. Mean change from baseline varied between increase and decrease between different time points, hampering firm conclusions. However, there seems to be no consistent and meaningful changes over time in laboratory parameters.

Occasional TEAE were reported in laboratory parameters. All TEAE but two (two events of vitamin D-deficiency) were deemed as unrelated by the investigator. Vitamin D decreased is already labelled in the SmPC for both the adult and paediatric population. One SAE was reported, elevated serum amylase in the subject with gallstone pancreatitis. Elevated serum amylase is expected with pancreatitis.

Two subjects developed transient antidrug antibodies (ADA) during the studies. Both subjects were negative for neutralising antibodies and no TEAE for injection site reactions or hypersensitivity were reported to coincide with the time point of the positive ADA test

The most up to date PSUR (#5, covering the period 19/2/20-18/8/20) did not identify any new safety concerns, with the majority of AEs reported are either expected ADRs with burosumab use and/or the underlying conditions being treated and the overall B/R remaining positive. The applicant has submitted a table summarising cumulative exposure post-marketing. A column in this table lists 98 patients as receiving burosumab under an EAP, including some TIO patients. Upon request, the MAH has clarified that the total number of patients with tumour-induced osteomalacia (TIO) exposed to burosumab in the post-marketing setting, calculated based on sales and marketing experience, cumulatively up to 31 July 2021 is 91 patients, with 90 adult patients and 1 adolescent patient (from commercial setting in the United

States). No additional post-marketing paediatric data in the TIO setting are available and therefore no paediatric safety concerns have been identified.

There is no safety database from clinical studies supporting the proposed maximum dose in adults with TIO; 2 mg/kg Q2W up to a maximum of 180 mg per administration. Only one single subject in the current TIO studies received this dose. Upon request, the MAH has summarised non-clinical data on potential safety concerns with high doses of burosumab. In a non-clinical study, adult monkeys were administered up to 30 mg/kg, which according to the MAH would correlate to a dose of 100 mg/kg in adult humans, for up to 40 weeks. There was no evidence of possible off-target toxicity, even at the highest dose. The dose limiting safety concern in animal studies was related to the on-target pharmacological effect, i.e., ectopic mineralisation of multiple tissues and organs (e.g., kidney, heart, lung, and aorta), and associated secondary consequences (e.g., nephrocalcinosis) in some cases. This was closely related to hyperphosphataemia and was observed in animals only at doses of burosumab that resulted in serum phosphate concentrations greater than approximately 8 mg/dL (2.6 mmol/L). This is already reflected with wordings in section 4.2 and 4.4 in the SmPC advising prescribers to target fasting serum phosphate in the lower end of the normal reference range for age and to monitor levels of fasting serum phosphate to minimise the risk of hyperphosphatemia. This is considered sufficient.
Upon request, the MAH has reiterated that there are no safety concerns limiting the maximum dose per administration in subjects with XLH to 90 mg. The use of two different levels for the maximum dose to be given at one administration is still not fully understood. Notwithstanding, as there are no indications of a safety issue at any of the different maximum doses, the issue is not further pursued.

In summary, there were no new and unexpected safety issues in the limited safety database of the TIO population compared to the known safety profile of Crysvita.

Assessment of paediatric data on clinical safety

No data are available on the use of burosumab in paediatric subjects. The proposed indication includes subjects from 1 years old and specific information on dose titration based on PK/PD modelling in paediatric subjects. The applicant comments that ADR profiles in paediatric and adult subjects in the XLH development program were in general comparable with few exceptions. This is reassuring, however, the lack of any safety data in this population represents an uncertainty. It must be acknowledged that the TIO population differs significantly from the XLH population in terms of heterogeneity of the underlying condition. Specifically, FGF23 levels and consequent hypophosphataemia are dependent on underlying tumour burden. No data have been submitted and limited information are available on disease progression in TIO paediatric patients.

The MAH was asked to discuss whether the differences in clinical manifestations of TIO between adults and children are likely to affect the extrapolation of safety data. In response, the MAH has presented a summary from a recent paper (Jiajue et al. 2021), summarising data from adolescents (age range 14-20 years) with TIO. In general, clinical manifestation in these cases was comparable to adults, though it should be noted that the majority of this cohort are adolescents rather than children. Serum FGF23 levels were modestly higher, though this may be related to normal age-related differences rather than differing pathology. It is also accepted that this a heterologous condition. A company sponsored literature search between 2006-2020 identified 42 cases of TIO in subjects under the age of 18 years, with none less than two years old.
It is agreed that based on the highly limited dataset available, there is no indication of any paediatric specific clinical manifestations of TIO raising specific concerns related to the extrapolation of safety data.

Upon request, the MAH has amended the SmPC to increase the frequency of serum phosphate measurements following initiation of treatment in paediatric TIO subjects to the same frequency as for XLH paediatric patients monitoring, i.e., every 2 weeks initially.

It is noted, based on the most recent PSUR (#5), that a post approval surveillance program in adult and paediatric patients with TIO has been agreed with the FDA. The MAH has agreed to provide information on the status of the Tumour-induced Osteomalacia Disease Monitoring Program (TIO DMP, study number UX023T-CL403) and a summary of the data evaluation as included in the Annual Progress Reports in the PSURs submitted in the EU.

2.5.2. Conclusions on clinical safety

The total safety data base in TIO subject comprises of 27 subjects with a total of 63 patient years. No paediatric subjects were included in the studies.

While it is acknowledged that this is an ultra-rare condition, the relatively low number of treated TIO subjects and the lack of placebo-controlled data as well as the absence of any safety data in TIO paediatric subjects renders the interpretation of the safety data generated problematic. In general, the safety profile of burosumab in the limited TIO safety data set presented is comparable to what has previously been reported in the XLH population. No indication of clinical manifestations specific for paediatric subjects with TIO compared to adults has emerged to date. Thus, no specific concerns related to the extrapolation of safety data from the adult TIO population have been identified.

There is no safety database from clinical studies supporting the proposed maximum dose in adults with TIO; 2 mg/kg Q2W up to a maximum of 180 mg per administration. Only one single subject in the current TIO studies received this dose. However, in animal studies, there was no evidence of possible off-target toxicity, even at the highest dose. The dose limiting safety concern in animal studies was related to the on-target pharmacological effect, i.e., ectopic mineralisation. This is already reflected with wordings in section 4.2 and 4.4 in the SmPC advising prescribers to target fasting serum phosphate in the lower end of the normal reference range for age and to monitor levels of fasting serum phosphate to minimise the risk of hyperphosphatemia. This is considered sufficient.

In summary, there were no new and unexpected safety issues in the limited safety database of the TIO population compared to the known safety profile of Crysvita.

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 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.0 is acceptable.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated to reflect the extension of the indication to the TIO population. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all proposed changes to the Product Information and the assessor comments.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

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 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

Tumour-induced osteomalacia (TIO) is a rare, serious, and debilitating condition caused by overproduction of fibroblast growth factor 23 (FGF23) by a tumour. The causative tumours are typically phosphaturic mesenchymal tumours (PMTs), a heterogeneous set of bone and soft tissue tumours that have a distinct histological appearance.
The incidence of TIO is not established; however, the MAH cites a recent study from Europe, indicating an incidence of approximately 0.1/100,000 per person year in Denmark. In the literature, around 500 reports of TIO have been published.

High levels of circulating fibroblast growth factor 23 (FGF23) leads to excessive urinary phosphate excretion and subsequent hypophosphataemia, resulting in defective bone mineralisation with osteomalacia, fractures and bone deformities requiring surgical intervention.

3.1.2. Available therapies and unmet medical need

When possible, tumour resection is the first line of treatment for TIO and can be curative. However, identifying the location of the causative tumour is often difficult, despite functional and anatomical imaging. Approximately 35% to 40% of patients with TIO have tumours that cannot be localised and therefore cannot be surgically excised. Furthermore, concomitant medical conditions and/or risk factors may preclude surgery in some subjects. When the tumour cannot be located or when complete resection is not possible, medical treatment should be initiated.

There is no approved or available therapy that specifically treats the underlying pathophysiology of elevated FGF23-induced hypophosphataemia in TIO in subjects in whom the underlying tumour could not be located or resected. Current medical management includes supplementation therapy with multiple daily doses of oral phosphate and/or active vitamin D analogues. The phosphate dose required to improve clinical symptoms is often limited by intolerable gastrointestinal side effects and the rapid phosphate

homeostasis requires multiple daily administrations. In some cases, active vitamin D alone may be administered.

Oral phosphate/active vitamin D therapy does not correct renal phosphate wasting, the underlying cause of hypophosphataemia, and resultant osteomalacia. In addition, oral phosphate therapy may exacerbate phosphate wasting by increasing the renal phosphate load since the impairment in renal phosphate reabsorption due to excess FGF23 is not addressed. The intermittent phosphate load also triggers high urinary phosphate excretion and increases the risk and progression of nephrocalcinosis and nephrolithiasis. In some instances, the compensatory increases in parathyroid hormone (PTH) may increase the risk of developing secondary or tertiary hyperparathyroidism, which in turn can lead to hypercalciuria, and thereby further increase the risk of nephrocalcinosis. As such, oral phosphate/active vitamin D treatment requires frequent monitoring to mitigate the risks of nephrocalcinosis, hypercalciuria, and hyperparathyroidism.

More efficacious, safer, and convenient therapies are clearly needed for patients who experience FGF23-related hypophosphataemia in tumour-induced osteomalacia in subjects with TIO with tumours that cannot be localised or surgically resected.

3.1.3. Main clinical studies

The MAH has provided two studies to support the efficacy of burosumab in the treatment of TIO in adult subjects, UX023T-CL201 and KRN23-002. No studies have been performed in paediatric subjects with TIO.

UX023T-CL201 was an open-label, single arm, multicentre, Phase 2 study in adult subjects (≥18 years) with TIO or ENS-associated osteomalacia with fasting serum phosphorus level < 2.5 mg/dL (<0.81 mmol/l) in the United States. The study included an initial 48-week Treatment Period followed by a Treatment Extension Period for a total treatment duration of up to 300 weeks. Efficacy and safety data are presented through 144 weeks of treatment.
In this study, 14 subjects with TIO were included.

KRN23-002 was an open-label, single arm, multicentre, Phase 2 study in adult subjects (≥18 years) with TIO or ENS-associated osteomalacia with fasting serum phosphorus level < 2.5 mg/dL (<0.81 mmol/l) in Japan and South Korea with treatment up to 144 weeks.
Study KRN23-002 included 13 subjects with TIO.

Although both studies were designed to also include subjects with Epidermal nevus syndrome (ENS)-associated osteomalacia, given the rare nature of this disease, only one subject with ENS-associated osteomalacia was enrolled in Study UX023T-CL201 and none in KRN23-002. No claims regarding ENS have been made in the current procedure.

3.2. Favourable effects

Serum phosphate

- 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 (2 weeks after dosing), as averaged across dose cycles between Baseline and Week 24 was a *Co-primary endpoint in UX023T-CL201 and a secondary endpoint in KRN23-002*.
    - UX023T-CL201: 7/14 subjects; 50% (95% CI 26.8, 73.2)
    - KRN23-002: 9/13 subjects; 69% (95% CI not available)

- Mean change in Serum Phosphate Concentration Averaged Across the Midpoint of Dose Cycles (Weeks 0-24) was *Secondary endpoint in both studies*.
    - UX023T-CL201: Mean (SD) serum phosphate concentration increased from 1.60 (0.47) mg/dL at baseline to 2.64 (0.76) averaged across the midpoint Week 0-24 corresponding to a mean percentage change (SD) from baseline of +69.8 (43.7) %.
    - KRN23-002: Mean (SD) serum phosphate concentration increased from 1.62 (0.49) mg/dL at baseline to 2.63 (0.86) averaged across the midpoint Week 0-24 corresponding to a mean percentage change (SD) from baseline of +62.9 (41.2) %.
- Mean change in Serum Phosphate Concentration Averaged Across the Endpoint (pre-dose) of Dose Cycles (Weeks 0-24) was *Secondary endpoint in KRN23-002*.
    - UX023T-CL201: Mean (SD) serum phosphate concentration increased to 2.15 (0.57) averaged across the endpoint (pre-dose) Week 0-24 corresponding to a mean percentage change (SD) from baseline of +38.6 (33.0) %.
    - KRN23-002: Mean (SD) serum phosphate concentration increased to 2.43 (0.65) averaged across the endpoint (pre-dose) Week 0-24 corresponding to a mean percentage change (SD) from baseline of +53.2 (33.8) %
- Last available mean (SD) Serum phosphate (trough values)
    - UX023T-CL201: 2.57 (0.30) mg/dL (Week 240; n=7)
    - KRN23-002: 2.70 (0.46) mg/dL (Week 176; n=8)

Bone histomorphometry

The absolute change from Baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of KRN23 treatment using histomorphometric indices was a *Co-primary endpoint in UX023T-CL201 and a secondary endpoint in KRN23-002*.

- UX023T-CL201
    - Osteoid thickness: -5.1 um (-10.0, -0,2) (p=0.0428)
    - Osteoid surface/bone surface: -0.2% (-13.9, +13.5) (p=0.9770)
    - Osteoid volume/bone volume: -5,5% (-11.9, +0.9) (p=0.0858)
    - Mineralization lag time: There was a trend towards improvement; however, Mlt was readable at both baseline and Week 48 for only three subjects in UX023T-CL201. For the remaining eight subjects, Mlt data was imputed. These data are not considered assessable.
- In study KRN23-002, bone biopsies were optional. Data was provided for three subjects only.

Fracture data

Number of new fractures during burosumab treatment in UX023T-CL201:

- Week 24: 19
- Week 48: 17
- Week 96: 3

- Week 144: 3

Re-read data

	Baseline (Fractures/pseudofractures)	W 144 (Fractures/pseudofractures)
UX023T-CL201		
X-ray	36	18
Bone scan	81	37
KRN23-002		
Bone scan	39	16

Functional Mobility Tests

Data is given as LS mean (SE [UX023T-CL201] or SD [KRN23-002]) change from baseline at Week 48. No nominal p-value provided for KRN23-002.

- UX023T-CL201
    - 6-minute walking test: +25.5 (16.6) m; p=0.124
    - Sit-to-stand test: +1.6 (0.5) repetitions, p=0.0012
- KRN23-002
    - 6-minute walking test: + 57.5 (42.8) m
    - Sit-to-stand test: +3.9 (4.2) repetitions

3.3. Uncertainties and limitations about favourable effects

There are major limitations with the data presented to support the indication to treat FGF23-related hypophosphataemia in tumour-induced osteomalacia.

In total, not more than 27 subjects were enrolled in the two studies in the application to extend the indication for Crysvita to include treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised, in patients aged 1 year and over.

After the data cut off for the initial submission for the current variation at Week 144/88, the number of subjects active in the study decreased markedly. Only 4/27 subjects seem to adhere to treatment until the end of the studies. the MAH has clarified that this was in large part due to that per study protocol, the study duration differed depending on whether subjects transitioned off the study to receive commercial burosumab treatment when it became available in their territory. For the remaining subjects discontinuing the study, it is agreed with the MAH that the vast majority could be considered unrelated to treatment.

No TIO subject under the age of 18 years have been treated with burosumab in the clinical studies. There is very limited data on burosumab treatment in paediatric subjects, mostly adolescents, with TIO from case reports in the literature and post-marketing data from the US and Japan. In the US, burosumab is approved for treatment of TIO in subjects from the age of two years. The MAH has clarified that the

higher age limit in the US was based on lack of data rather than specific safety concerns. Moreover, the MAH state that there is safety data available from one year of age in the XLH population to support the safe use of burosumab safety in this age cohort.

The dosing regimen for the paediatric population was evaluated by modelling and simulation that extrapolated adult population PK and PK/PD models to paediatric age groups. It is reasonable to assume that the PK/PD of burosumab would be similar in paediatric patients to that in adult patients with TIO, and that any potential differences in the PD relationship between adults and paediatrics is likely to be captured by the proposed weight-based posology of burosumab.

In the posology for the TIO indication, the MAH proposes the same starting dose as used in the studies, i.e., 0.3 mg/kg Q4W, and a maintenance dose up to 2 mg/kg Q4W or even Q2W (maximum 180 mg per administration). The proposed starting dose in the paediatric TIO population is 0.4 mg/kg for subjects ≤12 years of age and 0.3 mg/kg for subjects >12 years of age. The approved starting dose for adult subjects with XLH is 1 mg/kg. No maximum weight-based dose in adults with XLH is provided in the SmPC; however, the maximum absolute dose is 90 mg per administration, restricting the dose to approximately 1.3 mg/kg in a subject weighing 70 kg.

For none of the studies was there a prospective discussion on a minimum required level of efficacy for the study to be interpreted as successful and analyses were conducted without any consideration concerning multiplicity. The open label nature of both studies without an adequate control in a small number of patients where a priori statistical criteria of success had not been clearly defined in the presence of potential confounding were, and still are, major deficiencies that limits interpretation of the primary and secondary endpoints efficacy results. The resulting inferences from the provided study data can only be considered as preliminary and not confirmatory. This conclusion has not changed albeit will not be further pursued.

Moreover, there is substantial heterogenicity among subjects with TIO, leading to complexity of the study results. Differences in disease severity and duration, levels of FGF-23, dosing and compliance with oral phosphate/active vitamin D treatment prior to study entry contribute to this heterogenicity.

Regarding potential confounding the MAH's reply was far from adequate, and the Applicant was again requested, for both studies (KRN23-002 and UX023T-CL201), to address the impact of confounding on the observed results, in particular the primary and secondary outcome. By now, the MAH's has provided some evidence of the impact of covariates/potential confounders on outcomes. The analyses do not provide an equivalent estimate of a treatment effect in the context of comparative evidence due to the limitation of the design, being a single arm trial. Consequently, the matter is partially resolved, but not pursued further as definitive evidence of an unbiased effect as a consequence of confounding would be very difficult to derive.

The studies were not designed to show efficacy against standard of care for the condition, i.e. active Vitamin D and/or phosphate. The lack of comparator is considered a major weakness with the TIO development program.
The MAH argues that the lack of control group could be compensated by the vast majority of subjects being treated with Vitamin D and/or phosphate before entering the study. Per the study protocols, active treatment with oral phosphate substitution and active Vitamin D should be withdrawn at least two weeks prior to the screening visit. As such previous treatment was not an eligibility criterion for the studies, no earliest time for withdrawal of conventional therapy was identified. In Study UX023T-CL201, subjects were without oral phosphate and vitamin D therapy for at least 6 weeks, and in Study KRN23-002, subjects were without oral phosphate and vitamin D treatment for at least 8 weeks. However, actual screening periods varied for each subject. Oral phosphate is normally given 3-5 times daily, as serum phosphate is rapidly regulated in the body, precluding that serum phosphate levels would be sustained several weeks or months after withdrawal of conventional therapy.

The MAH has provided a summary of the last regular serum phosphate measurement before entering the study for comparison to study measurements. Data is difficult to interpret as regular measurements were only available for in total 17 subjects (UX023T-CL201: n=8; KRN23-002: n=9), the time between the last regular serum phosphate measurement and the baseline measurements varied greatly, and, at least in study UX023T-CL201, this time was generally several months long. Furthermore, only one pre-withdrawal phosphate measurement was available for each subject. Nevertheless, a numerical decrease in mean serum phosphate of approximately 0.5 mg/dL was seen between last regular measurement and baseline. As the phosphate co-primary analysis in study UX023T-CL201 was not a comparison to baseline phosphate levels, this is not considered to impact the primary endpoint. For KRN23-002, the primary endpoint was "Serum phosphorus concentrations at each test timepoint"; however, only descriptive statistics were applied. The MAH has presented updated graphs with a "pre-withdrawal" timepoint in the SmPC.

As described in detail elsewhere, the original readers of the (pseudo)fracture data had access to prior radiographs and scans in order to assess the evolution of individual fracture and pseudofracture healing but were blinded to patient medical history and the study design. Due to the open label single arm study design, the risk of bias is considered substantial if the radiographs were read in pairs. To overcome this, the MAH has undertaken a re-read of all available images (bone scans and X-rays) by an independent reading centre. Images were assessed without reference to baseline images and were provided to the reader in a random order. The reader was tasked with assessing each bone scan and X-ray to identify the presence of fractures or pseudofractures. The number of fractures is low, resulting in small and sometimes contradictory results when comparing the effect of burosumab on single fracture locations between the studies and between the modalities. Notwithstanding, there was, as in the original reads, a consistent decrease in the total number of fractures and pseudofractures after initiation of burosumab in both studies and with both modalities also in the re-read. A reduction in both the number of patients reporting symptomatic fractures as adverse events and in the number of fractures reported in UX023T-CL201 was seen after initiation of burosumab treatment. Taken together, numerically, from the blinded re-reads, there seems to be a decrease in fractures with initiation of burosumab treatment.

Patient-reported symptoms are considered of limited value in open label studies. Furthermore, the subjects had been off conventional treatment with active Vitamin D and/or oral phosphate for several weeks at baseline. This may have worsened physical performance and thereby the reported HRQL at baseline, which in turn may raise expectations of resumed treatment. The patient-reported outcomes, albeit in support for the proposed indication, needs to be interpreted with caution.

3.4. Unfavourable effects

Fatal events

Two fatal events were reported in Study UX023T-CL201, one during the course of the study and one after Week 144.

- One Subject died at study day 358 from cardiac arrest in conjunction respiratory failure and septic shock following gallstone associated pancreatitis and cholangitis.
- One Subject, >70y, died at day 1450 from multiorgan failure and disseminated ovarian cancer diagnosed approximately one month before the fatal event.

None of the events were deemed as related by Investigator/Sponsor.

Treatment emergent adverse events (TEAE)

- UX023T-CL201
    - Subjects with any TEAE (n [%]): 14 (100%)
    - Subjects with related TEAE (n [%]): 9 (64%)
- KRN23-002
    - Subjects with any TEAE (n [%]): 12 (92%)
    - Subjects with related TEAE (n [%]): 5 (38)

The most common TEAEs reported (≥ 20% of subjects) included nasopharyngitis (44.4%), arthralgia (37.0%), pain in extremity (37.0%), upper respiratory tract infection (25.9%), and cough (22.2%).

Related TEAEs that were reported for at least two subjects across studies included injection site reaction, hyperphosphataemia, vitamin D deficiency and rash

The spectrum of TEAE was similar between the adult XLH and TIO populations. The number of related TEAE was higher in the TIO populations compared to the adult XLH population; however, the mean age was substantially higher in the two studies in the TIO population compared to the pivotal adult XLH study.

Serious adverse events (SAE)

- UX023T-CL201
    - Subjects with any SAE (n [%]): 7 (50%)
    - Subjects with related SAE (n [%]): 0
- KRN23-002
    - Subjects with any SAE (n [%]): 4 (31%)
    - Subjects with related SAE (n [%]): 0

More subjects in the TIO versus the XLH population reported a SAE (41% vs 16%, respectively); however, none of the SAE were deemed as related.

In total, ten subjects over the two studies reported at least one SAE associated to the SOC neoplasm. In six subjects, the events were related to a pre-existing mesenchymal tumour. In one subject, the lesion (meningioma) was identified several years before study start. For the remaining three subjects (PT Large Intestine Polyp [2] and disseminated ovarian cancer), the respective neoplasms were diagnosed during the course of the studies. None of these events were deemed as related by the Investigator/sponsor.

Three subjects (11%) reported a SAE of septic shock. There was nothing remarkable in the narratives of the three events and the events were deemed as unrelated.

Prespecified Events to Monitor

Prespecified Events to Monitor for burosumab are Injection site reaction, Hypersensitivity, Hyperphosphataemia, Ectopic mineralisation and Restless leg syndrome:

- Injection site reaction 4/27 (15%)
- Hypersensitivity 6/27 (22%)
- Hyperphosphataemia 2/27 (7%)
- Ectopic mineralisation 3/27 (11%)

- Restless legs syndrome 2/27 (7%)

The total exposure-adjusted event incidence for the Prespecified Events to Monitor was generally somewhat higher in the TIO populations compared to the adult XLH population.

Two events of hyperphosphataemia were reported: one in a subject with serum phosphate in the normal range before initiating burosumab and one in subject receiving radiation therapy against the underlying tumour.

Antidrug antibodies (ADA)

Two subjects developed transient antidrug antibodies (ADA) during the studies. Both subjects were negative for neutralising antibodies and no TEAE for injection site reactions or hypersensitivity were reported to coincide with the time point of the positive ADA test

3.5. Uncertainties and limitations about unfavourable effects

The maximum burosumab dose in adults with TIO according the proposed SmPC was 2 mg/kg Q2W with an absolute maximum dose of 180 mg per administration. In Study KRN23-002, no subject was given a higher dose than 1.8 mg/kg and no subject was given an absolute dose of 180 mg on any occasion.

In Study UX023T-CL201, only one subject used the maximum dose (2 mg/kg); however, another subject also reached the maximum absolute dose of 180 mg. For one subject (the subject given the 2 mg/kg dose), the option to administer burosumab Q2W was used. Thus, there is no safety database from clinical studies supporting this dose, not even from the current TIO studies. The total safety data base in TIO subject comprises of 27 subjects with a total of 63 patient years. It is accepted that this is an ultra-rare condition, however, the relatively low number of treated TIO subjects and the lack of placebo-controlled data as well as the absence of any safety data in TIO paediatric subjects makes the interpretation of the safety data generated difficult.

3.6. Effects Table

Table 46: Effects Table for Crysvita in the treatment of TIO

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
Responders	Please see notes*	n/N % (95% CI)	7/14 50 (26.8, 73.2)		UX023T-CL201
			9/13 69 (not available)		KRN23-002
Midpoint phosphate	Please see notes **	mg/dL %	+1.04 (0.56) +69.8 (43.7)	Baseline represent "off treatment" with active vitamin D/phosphate	UX023T-CL201
			+1.00 (0.64) +62.9 (41.2)	As above	KRN23-002
Endpoint phosphate	Please see notes ***	mg/dL %	+0.55 (0.43) +38.6 (33.0)	As above	UX023T-CL201
			+0.81 (0.49) +53.2 (33.8)	As above	KRN23-002
Bone biopsy	Please see	%	O.Th: -31	Unclear level of	UX023T-

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
	notes^		OS/BS: 0 OV/BV: -32	minimal clinically relevant improvement	CL201
6MWT	Walking distance during six minutes (change from baseline)	Meter	+25.5 (16.6)	p=0.124	UX023T-CL201
			+ 57.5 (42.8)		KRN23-002
STS	Repetitions per 30 sec (change from baseline)	Number	+1.6 (0.5)	p=0.0012	UX023T-CL201
			+3.9 (4.2)		KRN23-002
Unfavourable Effects					
Fatal events		n/N %	2/27 7%	None of the events deemed as related.	Pooled data
SAE		n/N %	11/27 41%	None of the events deemed as related	Pooled data
		n/N %			Pooled data

Abbreviations: O.Th Osteoid thickness; OS/BS osteoid surface/bone surface; OV/BV Osteoid volume/bone volume; 6MWT 6-minute walking test; STS Sit-to stand test

Notes:

* Responders: 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 (2 weeks after dosing), as averaged across dose cycles between Baseline and Week 24

** Midpoint phosphate: Mean (SD) change in Serum Phosphate Concentration Averaged Across the Midpoint of Dose Cycles (Weeks 0-24) (mg/dL and %)

*** Mean change in Serum Phosphate Concentration Averaged Across the Endpoint (pre-dose) of Dose Cycles (Weeks 0-24)

^ The change from Baseline in excess osteoid based on analysis of iliac crest bone biopsies after 48 weeks of KRN23 treatment using histomorphometric indices

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Low serum phosphate caused by uncontrolled production of FGF-23 from Phosphaturic mesenchymal tumours (PMT) is the main laboratory abnormality of TIO. The negative consequences of longstanding hypophosphataemia on skeletal health and quality of life are well known. Hypophosphatemia caused by TIO in adults results in many structural and metabolic consequences that contribute to a complex array of symptoms, especially stiffness and pain, as well as poor mineralisation with subsequent fractures/pseudofractures which together cause a decrease in physical function and mobility, leading to substantially impaired overall health.
Despite conventional treatment with active Vitamin D and/or oral phosphate, phosphate levels remained

low, bone pain persisted, and bone mineral density decreased significantly in many subjects with PMTs that could not be localised or are not accessible to surgery. The unmet medical need and burden of disease in this population is therefore fully acknowledged.

Studies UX023T-CL201 and KRN23-002 have shown that burosumab administration significantly improved serum phosphorus levels and that phosphate control was maintained with burosumab treatment over time. Serum phosphate, being a surrogate pharmacodynamic marker for clinical effect, could be questioned as the most important clinical endpoint, but chronic hypophosphataemia is a major contributor to the pathophysiology of the disease as described above. It is anticipated that normalisation of serum phosphate has a beneficial effect on bone calcification. 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 magnitude of increase in serum phosphorus concentration shown with burosumab treatment is considered clinically relevant. The increase in serum phosphate was accompanied by a sustained increase in phosphate reabsorption (TmP/GFR), and serum 1,25(OH)2D levels in both studies, supporting the primary analysis.

The Applicant has presented data in support of beneficial effects, shown by statistical significance or as numerical trends favouring burosumab, on bone mineralisation, functional mobility and strength, the number of new (pseudo)fractures and quality of life in both studies. The true extent of these improvements, and whether they will be maintained over the long-term or not, is still unclear. The study population in studies UX023T-CL201 and KRN23-002 is very limited and there are major limitations of the study design and study conduct, giving partly modest and inconsistent results, as described above.

With this said, the difficulties to conduct scientific studies in an ultra-rare disease as TIO, with approximately 500 published cases worldwide, are acknowledged. Differences in disease severity and duration, levels of FGF-23, dosing and compliance with oral phosphate/active vitamin D treatment prior to study entry are additional obstacles which likely have contributed to the complexity of the study results. In this context, the positive trends and numerical improvements in fracture data, bone mineralisation and Quality of life, albeit not fully robust, can be considered supportive of a beneficial effect of burosumab on subjects with TIO associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised. The clinical benefit is further supported by case reports from the literature and individual testimonies from study subjects reporting considerable improvements in signs and symptoms of TIO since beginning treatment with burosumab.

In addition, although the underlying causes of TIO and XLH are unique, both conditions are characterised by elevated FGF23, resulting in excessive renal phosphate wasting by impaired phosphate reabsorption, reduced vitamin D synthesis, and chronic hypophosphataemia. Effects of similar magnitude on serum phosphate with burosumab treatment have been reported for both conditions, taking a more conservative starting dosing in the TIO study population into consideration. There are no indications that normalisation of serum phosphate would not lead to similar beneficial effect on e.g., bone mineralisation and quality of life in the TIO population as in the XLH population. The same limitations apply for TIO subjects with longstanding hypophosphataemia as for XLH subjects started on burosumab in adult age. In the light of the same and very specific pathogenetic mechanism in both conditions, extrapolation of efficacy results from the XLH studies in combination with the (less robust) results from the TIO study, is considered to support to the extended indication to *FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised, in children and adolescents aged 1 to 17 years and in adults*.

No paediatric patients were included in the TIO studies. However, burosumab is indicated in children with XLH from the age of one year. Given the mechanistic relationship with XLH, the safety profile from children and adolescents with XLH is considered possible to extrapolate to the paediatric TIO population.

There are also no indications from the very limited safety data base, that any specific safety issues should apply to the adult TIO population compared to the XLH population.

It is not agreed that baseline data in Studies UX023T-CL201 and KRN23-002 could be considered "on treatment" with conventional therapy. No direct comparisons to other treatments are therefore accepted. Notwithstanding, as pointed out above, many TIO patients have limited effect of active Vitamin D and/or oral phosphate. Furthermore, conventional treatment is administered as multiple daily doses, associated with high non-compliance in both adults and children that compromise their overall tolerability long term. Treatment is often associated with potential risks such as nephrocalcinosis, hypercalciuria and secondary hyperparathyroidism. The beneficial effect of burosumab on phosphate homeostasis in the TIO population is therefore considered of clinical relevance also in the absence of a comparator.

Overall, the adverse events presented from the pivotal adult patient study did not demonstrate a significantly differing safety profile in TIO relative to XLH subjects. However, the available safety data in the adult population are limited and there are no safety data in paediatric subjects. However, no new and unexpected safety concerns have emerged from Study UX023T-CL201 and KRN23-002 up to the end of the studies relative to the XLH population. No indication of clinical manifestations specific for paediatric subjects with TIO compared to adults has emerged to date. Thus, no specific concerns related to the extrapolation of safety data from the adult TIO population have been identified.

There is no safety database from clinical studies, neither in XLH nor TIO, supporting the proposed maximum dose in adults with TIO; 2 mg/kg Q2W up to a maximum of 180 mg per administration. Only one single subject in the current TIO studies received this dose.
Upon request, the MAH has summarised non-clinical data on potential safety concerns with high doses of burosumab. In a non-clinical study, adult monkeys were administered up to 30 mg/kg, which according to the MAH would correlate to a dose of 100 mg/kg in adult humans, for up to 40 weeks. There was no evidence of possible off-target toxicity, even at the highest dose. The dose limiting safety concern in animal studies was related to the on-target pharmacological effect, i.e., ectopic mineralisation of multiple tissues and organs (e.g., kidney, heart, lung, and aorta), and associated secondary consequences (e.g., nephrocalcinosis) in some cases. This was closely related to hyperphosphataemia and was observed in animals only at doses of burosumab that resulted in serum phosphate concentrations greater than approximately 8 mg/dL (2.6 mmol/L). This is already reflected with wordings in section 4.2 and 4.4 in the SmPC advising prescribers to target fasting serum phosphate in the lower end of the normal reference range for age and to monitor levels of fasting serum phosphate to minimise the risk of hyperphosphatemia. This is considered sufficient.
The discrepancy in posology between XLH, allowing a maximum absolute dose per administration of 90 mg, and TIO, allowing up to 180 mg is still not fully understood. Notwithstanding, the MAH has clarified that there have been no safety findings that would suggest that XLH patients should receive an overall lower maximum dose, capped at 90 mg and that the dosing merely reflects the maximum dose given in the studies. The issue is therefore not further pursued.

3.7.2. Balance of benefits and risks

It is acknowledged that there is a clear unmet need for additional treatments for patients with this rare condition of TIO with tumours that cannot be localised and therefore cannot be surgically excised.

Burosumab treatment has demonstrated a reversal of hypophosphatemia. The increase in serum phosphate levels were statistically significant and the magnitude considered to be of clinical relevance. The study population is extremely small and with substantial heterogenicity in disease severity, leading to large variations in statistical analyses and inconsistencies in the data. Statistical significance has not been shown for all secondary endpoints, and the data is not considered fully robust. However, improvements,

albeit partly modest, on fracture data, bone mineralisation and quality of life, has been presented. This is considered to support that normalisation of serum phosphate levels by burosumab have similar beneficial effects in inoperable TIO subjects as in the XLH population.

The safety profile of burosumab in the XLH population is considered manageable, provided recommendations monitoring of serum phosphate and ectopic mineralisation are observed. No indication of a different safety profile has emerged from the very limited safety database in the TIO population.

Therefore, the CHMP considers that, despite the well-recognised study limitations and the small data set, the totality of evidence is sufficient to support an extension of indication for Crysvita to include the treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged 1 year and over. The limitations of the studies are reflected in section 5.1

3.8. Conclusions

The overall B/R of Crysvita for the treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in in children and adolescents aged 1 to 17 years and in adults is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation 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 and IIIB

Extension of indication to include treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in children and adolescents aged 1 to 17 years and in adults, based on data from two ongoing open-label clinical studies, UX023T-CL201 and KRN23-002, in adults with TIO (144-week data and 88-week data are available, respectively). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly. An updated RMP version 6.0 was agreed during the procedure. Further, the MAH's request for one additional year of market protection was also agreed.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).

Appendix

1. CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies dated 23 June 2022.