23 April 2026
EMADOC-1700519818-3044024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: CRYSVITA

International non-proprietary name: Burosumab

Procedure No. EMA/VR/0000263400

Note

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

Table of contents

List of abbreviations

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
ADA	Anti-drug antibody
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
CHMP	Committee for Medicinal Products for Human Use
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
EOS	End-of-study
EOT	End of treatment
ET	Early termination
EU	European Union
FGF23	Fibroblast growth factor 23
iPTH	Intact parathyroid hormone
LPLV	Last patient last visit
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PD	Pharmacodynamic(s)
PHEX	Phosphate-regulating gene with homologies to endopeptidases on the X chromosome
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PopPK/PD	Population pharmacokinetics/pharmacodynamics
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
Q2W	Every 2 weeks
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Score
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TIO	Tumour-induced osteomalacia
US	United States
XLH	X-linked hypophosphataemia

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 27 March 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of X-linked hypophosphataemia (XLH) in paediatric patients from birth to less than 1 year of age for CRYSVITA, based on final results from study BUR-CL207; this is a phase 1/2 Open-label, Multicenter, Non-randomized Study to Evaluate Safety, Pharmacodynamics, Pharmacokinetics and Effect of Burosumab in Pediatric Patients from Birth to Less than 1 Year of Age with XLH; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

Information relating to orphan designation

Crysvita was designated as an orphan medicinal product EU/3/14/1351 on 15/10/2014 in the following indication: treatment of X-linked hypophosphataemia (XLH). In addition, Crysvita was designated as an orphan medicinal product EU/3/18/2011 on 16/04/2018 for 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 P/0411/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001659-PIP01-15-M06 was completed.

The PDCO issued an opinion on compliance for the PIP EMA/PE/0000228048. A PIP compliance statement is being claimed with the submission of this type II variation.

Information relating to orphan market exclusivity

Crysvita is currently the only medicinal product granted orphan designation for X-linked hypophosphataemia.

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.

Scientific advice and protocol assistance

The MAH did not seek Scientific Advice or Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	27/03/2025
Start of procedure:	26/04/2025
CHMP Rapporteur's preliminary assessment report circulated on:	19/06/2025
CHMP Rapporteur's updated assessment report circulated on:	17/07/2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	24/07/2025
MAH's responses submitted to the CHMP on:	21/11/2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	30/12/2025
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	n/a
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	29/01/2026
MAH's responses submitted to the CHMP on:	19/02/2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27/03/2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	16/04/2026
CHMP opinion:	23/04/2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

X-linked hypophosphataemia (XLH) is a genetic disease caused by loss of function mutations in the PHEX gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) leading to hypophosphataemia.

State the claimed the therapeutic indication

The MAH initially sought an extension of indication to include paediatric patients from birth to 1 year of age. Following the first CHMP assessment and the List of Questions, the applicant revised the proposed indication to patients from 1 month to 1 year of age, in line with the available clinical evidence.

The claimed indication is:

- CRYSVITA is indicated for the treatment of X-linked hypophosphataemia **in infants from 1 month to 1 year of age with hypophosphataemia (see section 5.1)**, in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.
- treatment of 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 changes to the second part of the indication were proposed.

Epidemiology

XLH is rare, with estimated incidence ranging from 1 in 60,000 to 1 in 20,000 live births (Burnett, 1964; Imel and Econs, 2005; Beck-Nielsen, 2009; Endo, 2015; Rafaelsen, 2016). It is the most common inherited form of rickets and the most common inherited defect in renal tubular phosphate transport (Holm 2012; Haffner, 2019).

Aetiology and pathogenesis

In the absence of a functional PHEX gene, release of FGF23 by osteocytes is greatly increased (Bonewald and Wacker, 2013). Excess production, and hence high levels, of circulating FGF23 causes excessive urinary phosphate excretion and resultant chronic hypophosphataemia, which leads to defective bone mineralisation and progressive musculoskeletal dysfunction if left untreated. This impacts daily functioning and health from early childhood through adulthood. Elevated FGF23 levels also suppress 1,25(OH)2D production, resulting in decreased intestinal absorption of calcium and phosphate (Sabbagh, 2008; Tiosano and Hochberg, 2009). The clinical symptoms of XLH usually become apparent during the first or second year of life (Carpenter, 2011; Linglart, 2014; Haffner, 2019).

Clinical presentation, diagnosis

The clinical manifestation of XLH in childhood can vary widely, from isolated hypophosphataemia to dental abscesses, raised intracranial pressure, craniosynostosis, and severe skeletal deformities, particularly of the lower limbs, that cause daily pain and impaired physical functioning, such that a young child may be severely limited in their daily activities and suffer lifelong disability, social stigmatisation and pain as these deformities become a permanent structure of their bones. Children with XLH often require several lower limb orthopaedic surgeries to correct bone

deformities (Tenenhouse and Econs, 2001; Carpenter, 2011; Holm, 2012; Linglart, 2014; Beck-Nielsen, 2019; Haffner, 2019; Laurent, 2021; Haffner, 2025). Other major pathologic consequences of XLH in the bone, which are also seen in adults, are rickets, osteomalacia, fractures and bone deformities requiring surgical intervention, joint abnormalities, and dental issues, significantly impacting physical function and quality of life (Berndt, 1996; Auray-Blais, 2016; Laurent, 2021).

Management

Conventional treatment for XLH consists of multiple daily doses of oral phosphate therapy often combined with active vitamin D metabolites (i.e., calcitriol and alfacalcidol). However, conventional treatment is only partially effective and does not specifically target the underlying pathophysiology of skeletal disease in XLH to prevent or improve many of its profound multisystem complications. In contrast, treatment with burosumab targets the underlying cause of hypophosphataemia (i.e., excess FGF23 levels), by binding to and inhibiting the excessive biologic activity of FGF23, without interfering with other aspects of calcium/bone mineral metabolism. A systematic review undertaken by authors of the new International XLH management guidelines stated that burosumab, compared with conventional treatment, probably prevents lower limb deformities (Ali, 2025).

In the EU, burosumab is currently approved for the treatment of XLH in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults. However, since XLH is a genetic disease affecting children from birth, initiation of treatment as early as possible (i.e., infants aged < 1 year) is particularly important to minimise the complications of the disease progressing into childhood and adulthood (Mäkitie, 2003). The objective of early treatment in children includes the correction of skeletal deformities, prevention of rickets and improvement of dental health and overall growth (Haffner, 2019; Laurent, 2021). The updated European XLH management guidelines recommend postponing surgery, if possible, in children with growth potential who are treated with burosumab because sustained straightening of legs is expected for at least 3 years after this treatment is initiated (Haffner, 2025).

Patients who received early and continuous vitamin D and phosphate supplementation during childhood presented less periodontal attachment loss than patients with late or incomplete supplementation; continued treatment during adulthood further improved the periodontal health (Duplan, 2017). Moreover, children with XLH present with normal length/height at birth, but their annual height increment begins to deviate from that of healthy children as early as 6 months of age, demonstrating the need for earlier treatment initiation in infants aged < 1 year (Cagnoli, 2017; Mao, 2020). Children who commence conventional treatment for XLH before 1 year of age achieve better adult height results compared to those who commence treatment after their first year of life, with similar data reported for the radiographic changes associated with rickets (Mäkitie, 2003).

These data from early initiation of conventional therapy suggest that treatment of infants aged < 1 year with burosumab, due to its proven ability to restore a physiological phosphate homeostasis by inhibiting high circulating FGF23 levels, may have a positive impact on their long-term health outcomes. The partial effectiveness of conventional XLH therapy (as demonstrated by the persistence of symptoms) and its known associated side effects along with the requirement of multiple daily oral administrations over several years, support the rationale that early initiation of treatment with burosumab could address the unmet medical need in infants aged < 1 year.

2.1.2. About the product

Burosumab (KRN23) is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the excess biological activity of FGF23. The aim of the therapy is to minimise the clinical consequences of the disease by restoring normal serum phosphorus levels.

2.1.3. The development programme

Study BUR-CL207 is included in the Paediatric Investigation Plan (PIP; EMEA-C4-001659-PIP01-15) for treatment in children from birth to less than 1 year of age with X-linked hypophosphataemia. The clinical development was done in alignment with the agreed PIP.

2.1.4. General comments on compliance with GCP

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

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

As the active substance burosumab is a monoclonal antibody, it is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 1: Interventional Burosumab Studies with Patients < 1 year of age

Study Name	Population
BUR-CL207: A Phase 1/2 Open-label, Multicenter, Non-randomized Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Burosumab in Pediatric Patients from Birth to Less than 1 Year of Age with X-linked Hypophosphatemia (XLH)	XLH patients 0 to < 1 year (N=16)

XLH=X-linked hypophosphataemia

Note: Study BUR-CL207 was part of the PIP.

2.3.2. Pharmacokinetics

The general pharmacology of burosumab was described in EMEA/H/C/4275/0000, where efficacy and safety of Crysvita were established in paediatric subjects ≥1 to ≤12 years old with X-linked hypophosphatemia (XLH). The clinical pharmacology data provided in support of the current

variation application originate from Study BUR-CL207. During treatment, the dose is titrated based on response.

Study BUR-CL207

Methods

Study BUR-CL207 was a non-randomised, open-label trial in paediatric patients from birth to <1 year of age with XLH. All enrolled subjects received burosumab. Subjects were enrolled into three cohorts: Cohort 1 (≥6 months to <12 months old) with a starting dose of 0.4 mg/kg Q2W, Cohort 2 (≥6 months to <12 months old) with a starting dose of 0.8 mg/kg Q2W, and Cohort 3 (<6 months old) with a starting dose of 0.4 mg/kg Q2W. Burosumab dosing was adjusted based on the PD response assessed by serum phosphate levels (measured every 2nd to every 4th week). If fasting serum phosphate was below the reference range for age, the dose was increased stepwise by 0.4 mg/kg up to a maximum dose of 2.0 mg/kg Q2W.

Blood samples for analysis of serum burosumab concentrations were collected predose and Days 7, 14, 28, 42±1, 56±1, 84±1, 112±1, 140±1, 182±1, 224±1, 280±1, 336±1 (EOT), and 392±1 (EOS). Blood samples for analysis of the presence of anti-drug antibodies (ADAs) were collected predose and Days 42±1, 112±1, 280±1, 336±1 (EOT), and 392±1 (EOS).

Serum samples were analysed for burosumab concentration using a validated electrochemiluminescence (ECL)-based immunoassay at BioAgilytix Labs, Durham, NC, USA. This bioanalytical method was previously assessed and found acceptable.

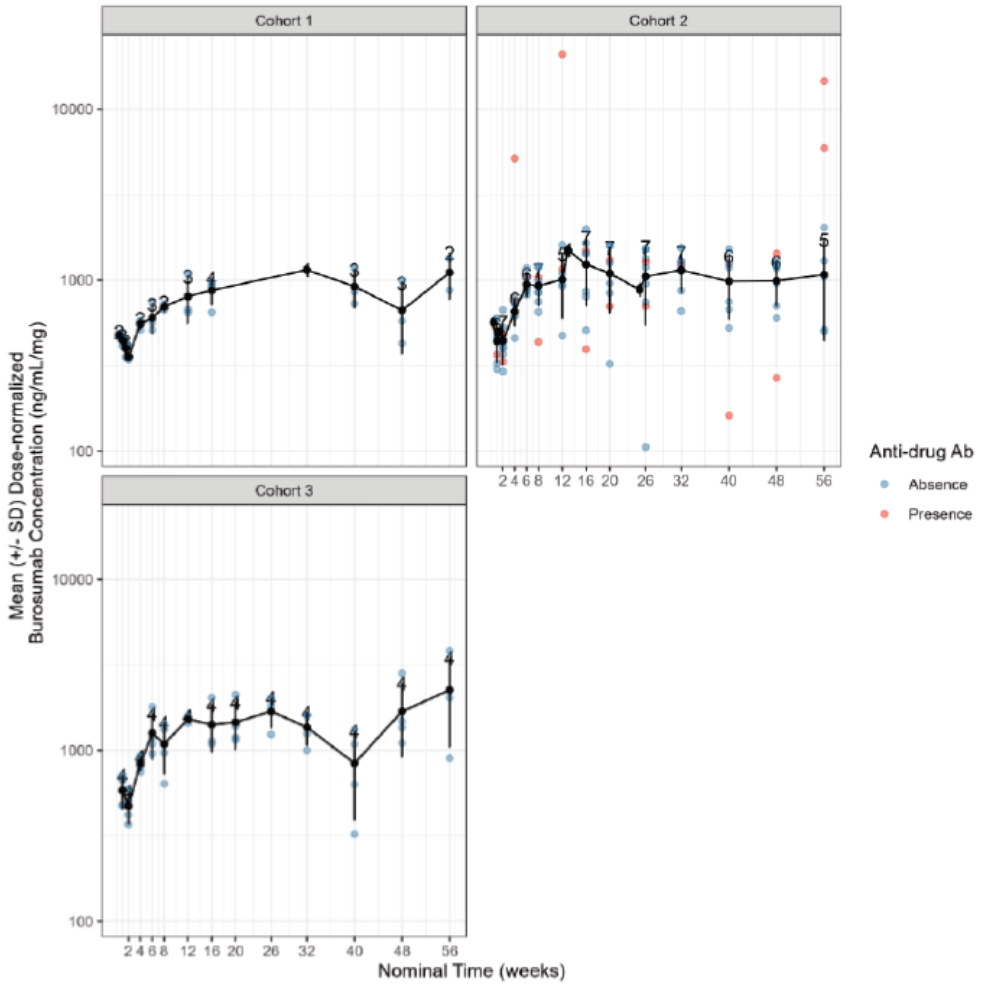
Serum samples were analysed for ADA using a validated ECL-based immunoassay at BioAgilytix Labs, Durham, NC, USA. Confirmed ADA-positive samples were further tested for neutralizing antibody (NAb) activity using a validated ECL-based immunoassay at Toray Research Center, Inc, Kamakura-shi, Kanagawa, Japan. These bioanalytical methods were previously assessed and found acceptable.

Results

A total of 16 subjects were enrolled in Study BUR-207: N=3 subjects to Cohort 1, N=9 subjects to Cohort 2, and N=4 subjects to Cohort 3. Median age at baseline was 36.4 weeks (range: 17.7 to 48.0 weeks). Median body weight at baseline was 8.25 kg (range: 6.2 to 10.8 kg).

Mean dose-normalised serum burosumab concentrations in Study BUR-CL207 are presented in Figure 1.

Figure 1. Mean (±SD) dose-normalised serum burosumab concentrations in Study BUR-CL207 by study cohort.



Ab= antibodies; ADA= antidrug antibody; SD= standard deviation (vertical segment line)
Note: Blue dots represent individual concentrations of serum samples without presence of ADA and red dots represent individual concentrations of serum samples with presence of ADA. The mean values are connected by line and the number of concentrations included in the calculation of the mean and SD are indicated for each time point.

Overall, 2 subjects had ADA-positive results during the study. One subject was ADA negative at screening visit and ADA positive at all post-baseline visits with ADA sampling; one subject tested positive for ADA at screening visit, Week 6, and Week 16 (also positive for Nab at Week 16), while inconclusive at other visits. For both subjects, the highest titer value observed was in the initial timepoint that returned the positive result, and the titer value subsequently decreased. Since the subject who tested positive for ADA at screening visit, did not have a boosted titer response post burosumab administration, the overall ADA response was considered negative for this subject. Other subjects who exhibited a mix of negative and inconclusive ADA results with increasing burosumab concentration over time were considered ADA-negative. Therefore, only 1 subject had positive ADA status.

Population PK analysis

The population PK analysis (KYOW-PMX_CRYSVITA-2631 report) was conducted to characterise the PK of burosumab in paediatric patients <1 year old with XLH, and to compare the burosumab PK between paediatric patients <1 year old and paediatric patients ≥1 year old.

Data

A total of 295 subjects with XLH treated with burosumab were included in the population PK analysis. Among these subjects, 22 were infants (one month to <2 years old, including 16 infants from Study BUR-CL207), 88 were children (2 to 12 years old) and 185 were adults (≥18 years). A summary of age and body weight at baseline across age cohorts is presented in Table 2.

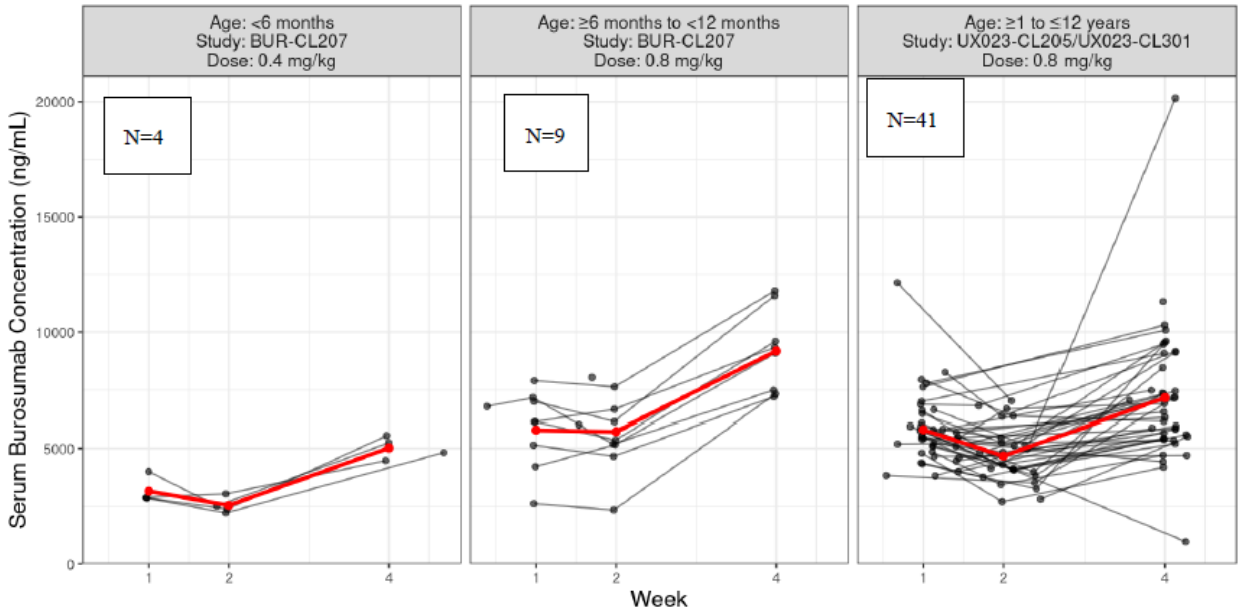
Table 2. Summary of continuous demographic data at baseline across age cohorts for subjects included in the population PK analysis.

Covariates	Mean (CV%) Median [Minimum, Maximum]				
	BUR-CL207 <12 months (N=16)	Infants* ≥1 month to <2 years (N=22)	Children From 2 to 12 years (N=88)	Adults ≥18 years (N=185)	Overall (N=295)
Age (years)	0.663 (28.2) 0.697 [0.340, 0.921]	0.837 (45.1) 0.779 [0.340, 1.80]	7.28 (38.7) 8.00 [2.20, 12.8]	40.6 (30.2) 41.0 [18.5, 68.0]	27.7 (70.4) 28.4 [0.340, 68.0]
Body weight (kg)	8.31 (14.8) 8.25 [6.20, 10.8]	8.92 (18.0) 8.85 [6.20, 12.7]	25.7 (41.4) 23.4 [9.20, 55.2]	71.7 (26.7) 69.0 [36.1, 140]	53.3 (54.8) 55.2 [6.20, 140]

*Including participants in study BUR-CL207.

After exclusion of pre-dose samples, a total of 3831 serum samples were available for the population PK analysis, of which 2% were below LLOQ and were excluded from the analysis. Amongst the 3735 samples included in the population PK analysis, data collected in infants represented 6.0% of the overall PK dataset, whereas data collected in children represented 28% of the overall PK dataset. A comparison of observed burosumab serum concentrations between paediatric patients aged ≥1 to <6 months, receiving 0.4 mg/kg Q2W (Cohort 3 in study BUR-CL207), paediatric patients aged ≥6 to <12 months, receiving 0.8 mg/kg Q2W (Cohort 2 in study BUR-CL207), and paediatric patients aged ≥1 to ≤12 years (studies UX023-CL205 and UX023-CL301) is presented in Figure 2.

Figure 2. Comparison of observed burosumab serum concentrations (ng/mL) between infants aged ≥1 to <6 months, infants aged ≥6 to <12 months, and paediatric patients aged ≥1 to ≤12 years.



Black lines represent individual serum burosumab concentration-time profiles; Red lines represent mean serum burosumab concentration-time profiles.

Model

A one-compartment disposition model with first-order SC absorption previously resulted in adequate goodness-of-fit of serum burosumab concentration-time profiles in adult and paediatric subjects (≥1 year old). Time-varying body weight was included as a covariate on relative clearance (CL/F) and relative volume of distribution (V/F) with power functions (allometric scaling) with estimated exponents. This model was used as a base model for the current analysis. Since the observed serum burosumab concentrations in paediatric subjects aged <1 year were underestimated by the base model, the model was adjusted by including age effects on CL/F and V/F. The age effect on CL/F was parameterised as a maturation function whereas the age effect on V/F was parameterised as a power function.

Parameter estimates of the final population PK model are presented in Table 3. The change in the parameter estimates for CL/F and V/F with full maturation was <5% compared to previous modelling of serum burosumab in subjects ≥1 year old. A visual predictive check (VPC) of the final model, stratified by age group (including BUR-CL207 separately), is presented in Figure 3.

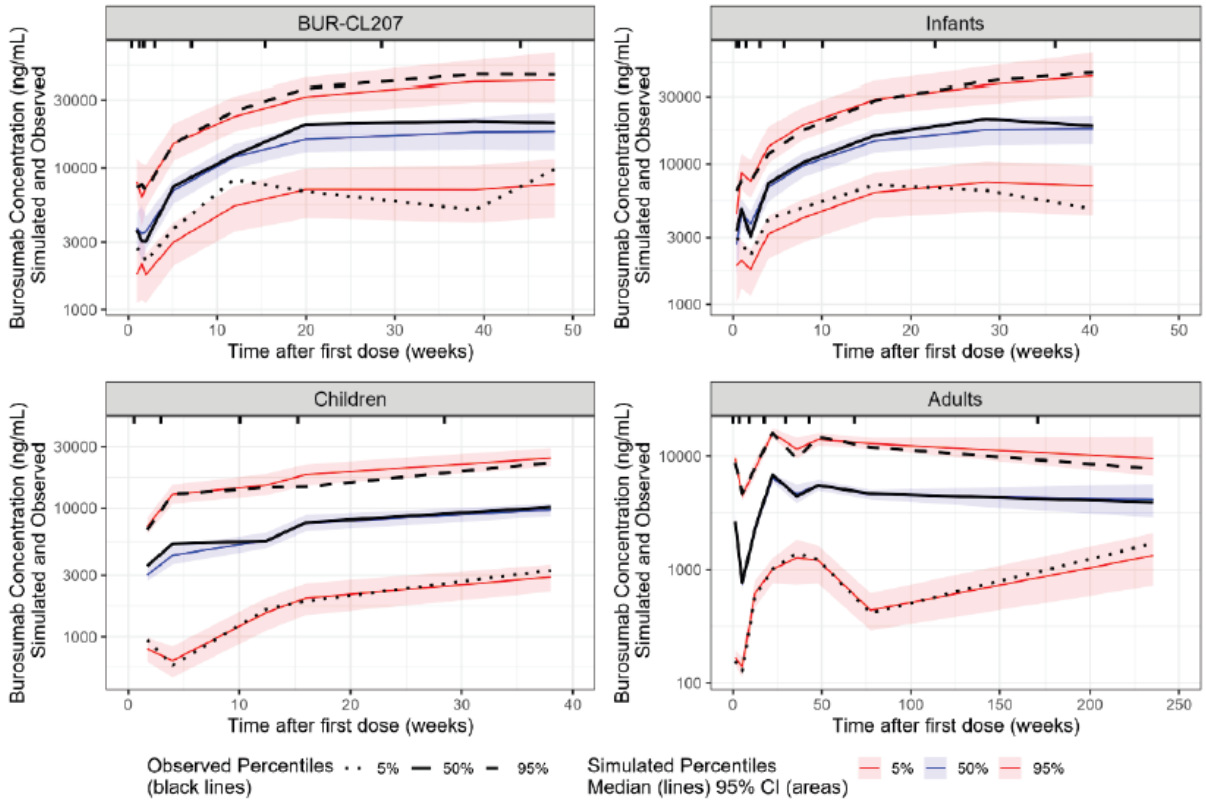
Table 3. Parameter estimates of the final population PK model.

Parameter	Typical Values	RSE (%)	95%CI	BSV (%) (RSE%)	Shrinkage (%)
Ka (1/day)	0.405	8.11	0.340, 0.469		
V/F (L)	7.23	5.87	6.22, 8.25	30.7 (8.35)	20.6
WT effect on V/F	$(WT/70\ kg)^{0.738}$	8.89	0.609, 0.866		
Time varying age effect on V/F	$(Age/28.4\ years)^{0.129}$	29.1	0.0552, 0.202		
CL/F (L/day)	0.279	2.53	0.265, 0.293	34.2 (8.69)	4.26
WT effect on CL/F	$(WT/70\ kg)^{0.805}$	6.11	0.709, 0.902		
Maturation β	0.250	35.5	0.0758, 0.424		
Maturation T_{CL} (years)	1.74	22.6	11.6, 30.2		
Additive error (ng/mL)	7.01	18.8	4.43, 9.60		
Proportional Error (%)	23.7	27.2	0.0208, 0.0469		

BSV= between subject variability; CI= confidence interval; CL/F= apparent clearance; Ka= absorption rate; popPK= population pharmacokinetic; RSE= relative standard error; T_{CL}= maturation half-life for CL/F; V/F= apparent central volume of distribution; WT= time-varying body weight; XLH = X-linked hypophosphatemia; β= fractional fold factor for clearance of full-term neonates

Note: $maturation = \left[1 - (1 - \beta) \times e^{-Age \times \frac{ln(2)}{TCL}}\right]$

Figure 3. Visual predictive check of the final model, stratified by age group (including BUR-CL207 separately).



Exposure predictions

Exposure metrics of serum burosumab were generated using individual post-hoc estimates from the final population PK model. Predictions were based on initial conditions as well as steady-state conditions, including age and body weight as measured at baseline and at the end of study, respectively. For the initial conditions, exposure following the first dose were predicted. For the steady-state conditions, exposure following burosumab Q2W dosing at the last dose received by each study subject were predicted. The descriptive statistics of individual burosumab exposure levels following the starting dose are presented in Table 4, and the descriptive statistics of individual burosumab exposure levels at the end of study, along with actual dose levels, are presented in Table 5, with stratification by age group. To enable a representative comparison at the starting dose, only subjects ≥1 year of age receiving the recommended starting dose are included in Table 4.

Table 4. Predicted exposure metrics following the starting dose, using individual post-hoc estimates in combination with the subjects' age and body weight at baseline.

PK parameter	Mean (CV%) Median [Minimum, Maximum] Geometric Mean (Geometric CV%)					
	BUR-CL207 Cohort 1 From 6 to <12 months (N=3)	**BUR-CL207 Cohort 2 From 6 to <12 months (N=9)**	**BUR-CL207 Cohort 3 From 1 to <6 months (N=4)**	**Infants From 1 to <2 years (N=6)**	**Children From 2 to 12 years (N=34)**	**Adults ≥18 years (N=150)**
Dosing regimen	0.4 mg/kg Q2W	0.8 mg/kg Q2W	0.4 mg/kg Q2W	0.8 mg/kg Q2W	0.8 mg/kg Q2W	1.0 mg/kg Q2W

C_{max} of burosumab (ng/mL)	2900 (7.4) 2940 [2670, 3090] 2890 (7.5)	6460 (30.8) 6470 [2760, 10500] 6150 (36.1)	3030 (12.7) 3010 [2590, 3510] 3010 (12.7)	5070 (20.9) 4890 [4080, 6910] 4990 (20.1)	5610 (19.8) 5300 [4170, 8980] 5510 (18.5)	7510 (26.5) 7470 [3600, 15000] 7260 (27.3)
C_{avg} of burosumab (ng/mL)	2300 (7.4) 2330 [2120, 2450] 2300 (7.5)	5110 (30.6) 5130 [2190, 8260] 4870 (35.9)	2400 (12.6) 2380 [2050, 2780] 2390 (12.6)	4000 (21.5) 3870 [3160, 5480] 3930 (20.8)	4400 (19.7) 4170 [3260, 6920] 4320 (18.5)	5900 (26.6) 5880 [2480, 11700] 5700 (27.5)
C_{last} of burosumab (ng/mL)	2630 (6.5) 2600 [2470, 2810] 2620 (6.5)	5920 (33.4) 5770 [2510, 10200] 5610 (37.4)	2880 (13.9) 2890 [2400, 3370] 2860 (14.1)	4290 (26.2) 4230 [3000, 6080] 4170 (26.4)	4480 (19.5) 4330 [3250, 6600] 4400 (19.0)	6140 (26.8) 6020 [1120, 12000] 5900 (29.8)

Table 5. Predicted exposure metrics at steady state, using individual post-hoc estimates in combination with the subjects' actual dose, age and body weight at the end of study.

	Mean (CV%) Median [Minimum, Maximum] Geometric Mean (Geometric CV%)				
PK Parameter	**BUR-CL207 < 1 year (N=16)**	**Infants > 1 month to < 2 years (N=22)**	**Children From 2 to 12 years (N=88)**	**Adults > 18 years (N=185)**	**Overall (N=295)**
Actual Burosumab Dose (mg)	11.7 (44.2) 12.4 [0.800, 22.0]	11.6 (38.6) 12.0 [0.800, 22.0]	36.4 (61.3) 30.0 [12.0, 90.0]	65.6 (32.5) 69.0 [8.10, 133]	52.9 (51.6) 51.0 [0.800, 133]
Last Dose	9.74 (92.2)	10.1 (75.5)	30.2 (69.2)	61.2 (43.6)	43.3 (83.6)
WT-adjusted Burosumab Dose (mg/kg)	1.12 (46.0) 1.19 [0.0708, 2.08]	1.06 (42.7) 1.04 [0.0708, 2.08]	1.03 (33.6) 0.912 [0.409, 2.04]	0.908 (22.9) 0.984 [0.100, 1.18]	0.955 (29.8) 0.976 [0.0708, 2.08]
Last Dose	0.926 (94.8)	0.916 (76.8)	0.976 (34.5)	0.869 (35.4)	0.903 (39.2)
C_{min} of Burosumab (ng/mL)	39053 (57.8) 32281 [2500, 79158]	32121 (70.0) 26466 [2500, 79158]	13430 (41.6) 12428 [3869, 38856]	14287 (40.5) 13627 [1055, 33653]	15362 (61.5) 13688 [1055, 79158]
	31191 (99.3)	24411 (101)	12374 (43.1)	12932 (53.1)	13382 (57.5)
C_{max} of Burosumab (ng/mL)	45177 (54.5) 38882 [2895, 88053]	37682 (64.9) 33443 [2895, 88053]	19234 (38.4) 18220 [7776, 51191]	18828 (36.1) 18389 [1645, 39836]	20355 (52.0) 18722 [1645, 88053]
	36517 (97.6)	29573 (93.7)	17958 (38.7)	17396 (46.0)	18271 (50.3)
C_{avg} of Burosumab (ng/mL)	42840 (55.6) 36062 [2745, 84691]	35552 (66.7) 30612 [2745, 84691]	16941 (39.3) 15950 [6153, 46398]	17056 (37.5) 16489 [1431, 37475]	18401 (55.1) 16688 [1431, 84691]
	34492 (98.1)	27605 (96.0)	15761 (39.9)	15666 (48.0)	16371 (52.3)
AUC of Burosumab (µg × day/mL)	600 (55.6) 505 [38.4, 1186]	498 (66.7) 429 [38.4, 1186]	237 (39.3) 223 [86.1, 650]	239 (37.5) 231 [20.0, 525]	258 (55.1) 234 [20.0, 1186]
	483 (98.1)	386 (96.0)	221 (39.9)	219 (48.0)	229 (52.3)
$T_{1/2}$ (day)	36.5 (30.8) 34.4 [17.7, 59.3]	32.0 (38.6) 30.3 [11.9, 59.3]	15.0 (22.0) 15.2 [7.77, 22.8]	19.8 (34.2) 18.5 [4.02, 64.0]	19.3 (40.3) 17.2 [4.02, 64.0]
	34.8 (32.8)	29.7 (42.3)	14.7 (23.2)	18.8 (32.8)	18.1 (36.3)

Note 1: Burosumab concentrations were derived based on the last burosumab dose at steady-state conditions.
Note 2: Subjects in Study BUR-CL207 were also included in the 'Infants' age group.
AUC=area under the serum concentration-time curve (over one dosing interval), C_{avg}=average serum concentration, C_{max}=maximum serum concentration, C_{min}=minimum serum concentration, CV%=coefficient of variation, N=number of subjects, PK=pharmacokinetic(s), $t_{1/2}$=elimination half-life, WT=body weight
Source: KYOW-PMX-CRYSVITA-2631 report, Table 6.

2.3.3. Pharmacodynamics

Please see *2.4 Clinical efficacy* for information on pharmacodynamic markers.

2.3.4. Discussion on clinical pharmacology

The clinical pharmacology data, provided in support of an indication in paediatric patients from birth to <1 year, originate from Study BUR-CL207. During treatment, the dose is titrated based on response. Potential differences in PK in paediatric patients <1 year of age compared to paediatric patients ≥1 year of age are hence of less concern as long as the starting dose accounts for such differences.

In Study BUR-CL207, the dose-normalised exposure appears to be higher in the youngest infants (Cohort 3; <6 months old) than in the older infants (Cohorts 1 and 2; ≥6 months to <12 months

old). Since the dose is titrated based on response (serum phosphate levels), a higher dose-normalised exposure may not be an issue. What is essential is that the actual exposure at the starting dose is safe, i.e. not higher than the exposure observed at the approved starting dose in paediatric patients ≥1 year of age, and that the titration scheme is adequate. In the study, the starting dose was lower in Cohort 3 (0.4 mg/kg Q2W) than in Cohort 2 (0.8 mg/kg Q2W), and Cohort 2 had the same starting dose as approved in paediatric patients ≥1 year of age. When comparing the actual exposure during the first 4 weeks of treatment (prior to any dose adjustment) across age, the observed concentrations in infants aged <6 months (Cohort 3) were initially lower than the observed concentrations in paediatric patients aged ≥1 to <12 years. However, at the end of the second dosing interval (4 weeks into treatment), the observed concentrations were within the concentration range observed in paediatric patients aged ≥1 to <12 years. For infants aged ≥6 to <12 months (Cohort 2), the observed concentrations were within the concentration range observed in paediatric patients aged ≥1 to <12 years, both after the first dose and at the end of the second dosing interval (4 weeks into treatment). However, at the end of the second dosing interval, the observed concentrations were in the upper end of the concentration range observed in paediatric patients aged ≥1 to <12 years.

There appears to be a difference in PK in paediatric patients <1 year of age, compared to paediatric patients ≥1 year of age and adults. In the final population PK model, body weight was included as covariate on both CL/F and V/F. However, body weight alone could not describe the observed differences. Therefore, age was also included as covariate on both CL/F and V/F. Estimation of correlated covariate effects is problematic, and the model should not be used to simulate exposure in subjects that were not included in the dataset. Despite the identified deficiencies, it was not considered necessary to update the population PK model. The descriptive performance of the model is acceptable, and it can adequately predict the exposure in subjects included in the dataset.

The differences in PK in paediatric subjects <1 year of age, compared to paediatric subjects ≥1 year of age and adults, may be a result of maturation of the immune system, affecting clearance, and/or a result of differences in the rate and extent of absorption, following subcutaneous administration to paediatric subjects <1 year of age compared to administration to older paediatric subjects and adults. Based on the final population PK model, the terminal elimination half-life is predicted to be approximately 35 days in infants aged <12 months, while it is predicted to be approximately 15 days in paediatric patients aged ≥2 to <12 years (see Table 5). An extended half-life leads to a larger accumulation and a longer time to reach steady state. Therefore, the exposure is expected to increase more in paediatric patients <1 year of age compared to paediatric patients ≥1 year of age, which means that the difference in exposure between infants aged ≥1 to <6 months receiving 0.4 mg/kg Q2W, and paediatric patients aged ≥1 to <12 years receiving the recommended starting dose of 0.8 mg/kg Q2W, is expected to decrease during repeated dosing. Furthermore, at steady state, the exposure in infants ≥6 to <12 months receiving 0.8 mg/kg Q2W is expected to be higher than the exposure in paediatric patients aged ≥1 to <12 years receiving the recommended starting dose of 0.8 mg/kg Q2W.

Predicted exposures (based on individual post-hoc estimates), based on initial conditions as well as steady state conditions, were provided. Given the length of the study (48 weeks of treatment), all subjects in Study BUR-CL207, also those enrolled in Cohort 3, were above 1 year of age in the predictions at steady state. When using the initial conditions (following the first dose), the predicted exposure was higher in paediatric patients aged ≥6 to <12 months receiving 0.8 mg/kg than in paediatric patients ≥1 year receiving 0.8 mg/kg.

For paediatric patients aged ≥1 to <6 months, the MAH proposes a starting dose of 0.4 mg/kg Q2W, a dose increment of 0.2 – 0.4 mg/kg during up-titration, and a maximum dose of 0.8 mg/kg Q2W. Despite the greater accumulation observed in paediatric patients aged ≥1 to <6 months, the MAH proposes to keep the same frequency of dose up-titration as in paediatric patients aged ≥1 year (i.e. not more frequently than every 4 weeks). Given the lower starting dose and maximum dose, the enablement of a smaller dose increment during up-titration, and the extended monitoring of fasting serum phosphate after treatment initiation and dose adjustment (fasting serum phosphate should be measured every second week for 6 weeks compared to every second week for the first month in paediatric patients aged ≥1 year), it is agreed that the risk of hyperphosphatemia is adequately controlled. Hence, the proposed starting dose, dose increment, and frequency of up-titration in paediatric patients aged ≥1 to <6 months are considered acceptable.

For paediatric patients aged ≥6 to <12 months, the MAH proposes a starting dose of 0.8 mg/kg Q2W, a dose increment of 0.4 mg/kg during up-titration, and a maximum dose of 2.0 mg/kg Q2W. Furthermore, the MAH proposes to keep the same frequency of dose up-titration as in paediatric patients aged ≥1 year (i.e. not more frequently than every 4 weeks). This is the same posology as recommended in paediatric patients aged ≥1 year. To support the proposed posology, the MAH presented observed data on serum phosphate in paediatric patients aged ≥6 to <12 months administered starting doses of ≥0.8 mg/kg Q2W (see Clinical safety). Based on these data, there were no indications that the proposed posology would cause hyperphosphatemia in paediatric patients aged ≥6 to <12 months. The extended monitoring of fasting serum phosphate after treatment initiation and dose adjustment (fasting serum phosphate should be measured every second week for 6 weeks compared to every second week for the first month in paediatric patients aged ≥1 year) further ensures an appropriate treatment; hence, the proposed starting dose, dose increment, and frequency of up-titration in paediatric patients aged ≥6 to <12 months are considered acceptable.

A population PK-PD analysis, describing the relationship between serum burosumab concentration and serum phosphate concentration, was provided (not presented). In the final PK-PD model, baseline age was included as a covariate on the baseline serum phosphate (E0), time-varying age was included as covariate on maximal response (Emax), and time-varying body weight was included as covariate on the concentration producing 50% of maximal response (EC50). Age-related effects on E0 and Emax are expected, given the change of normal levels of serum phosphate across age. However, a body weight related effect on EC50 was not expected and indicates a difference in the PK-PD relationship between paediatric patients <1 year of age compared to paediatric patients ≥1 year of age. Nevertheless, given that both the baseline concentration and the target reference range of serum phosphate is changing with age, and that the dose is titrated to achieve a serum phosphate concentration within the reference range, the modelling results should be interpreted with caution and the model is therefore not further described.

2.3.5. Conclusions on clinical pharmacology

During treatment with burosumab, the dose is titrated based on response. Potential differences in PK in paediatric subjects <1 year of age compared to paediatric subjects ≥1 year of age are hence of less concern as long as the starting dose and titration scheme accounts for such differences. Observed data indicate a longer terminal elimination half-life and greater accumulation in paediatric patients aged <12 months compared to paediatric patients aged ≥12 months. To mitigate the risk of hyperphosphataemia, a lower starting dose and smaller dose increments are

recommended for patients ≥1 to <6 months of age. In addition, extended monitoring has been introduced for all patients <1 year of age.

2.4. Clinical efficacy

2.4.1. Main study

BUR-CL207

A Phase 1/2 Open-label, Multicenter, Non randomized Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Burosumab in Pediatric Patients from Birth to Less than 1 Year of Age with X linked Hypophosphatemia (XLH).

Methods

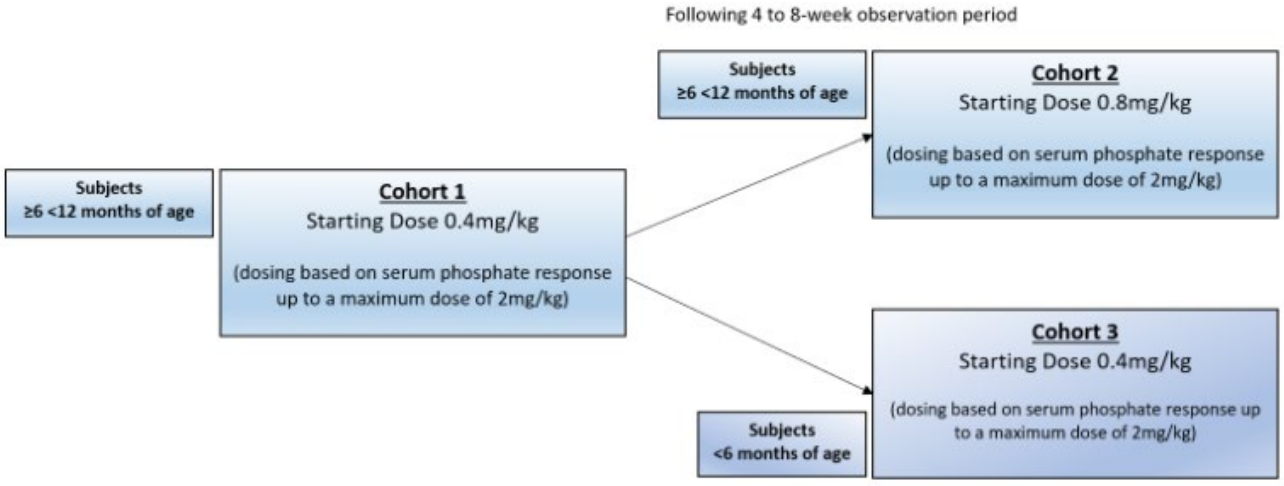
Study design

Study BUR-CL207 was a multicentre, open-label trial in paediatric patients from birth to < 1 year of age with XLH conducted in six European countries. All enrolled subjects received burosumab.

The study comprised a total treatment period of up to 48 weeks. The study enrolment plan comprised 3 cohorts, with 2 age groups (Cohort 1 and 2: from ≥6 months to <12 months; Cohort 3: <6 months of age) (Figure 4).

The observation period for decision to start Cohorts 2 and 3 was until the last subject enrolled in Cohort 1 completed 4 weeks of treatment; all available safety, PD, PK, and (when available) PK/PD relationship data were reviewed.

Figure 4: Study Diagram



DSMB=Data Safety Monitoring Board; PD=pharmacodynamic(s); PK=pharmacokinetic(s)
Note: A minimum of 3 subjects were planned to be enrolled in Cohort 1. The final number of subjects to be enrolled in each cohort was decided by the Sponsor's Medical Monitor and following DSMB recommendations. Following enrolment of the first 3 or 4 subjects in Cohort 3, an interim population PK/PD evaluation may have been performed to determine if the starting dose for the cohort could be increased to 0.8 mg/kg.

Study participants

Main inclusion criteria were

- Male or female paediatric subjects, aged <12 months at burosumab treatment initiation.

- Paediatric subjects with PHEX mutation or variant of uncertain significance in either the subject or a directly related family member with appropriate X-linked inheritance.
- Presenting serum phosphate levels below the age-specific LLN at Screening.

Exclusion criteria included Preterm paediatric patients with a chronological age of <6 months of age, renal impairment, nephrocalcinosis, and hypo- or hypercalcemia.

Treatments

The current approved and recommended starting dose of burosumab administered as a SC injection Q2W for the treatment of XLH with radiographic evidence of bone disease in paediatric patients 1 to 17 years of age with growing skeletons is 0.8 mg/kg.

Preliminary simulations have suggested that the 0.8 mg/kg starting dose can be extrapolated down to 6 months of age based on weight. However, kidney function in the paediatric population below 1 year of age, especially below 6 months of age, is not yet fully mature (i.e., GFR and function of tubules).

Thus, a starting dose of 0.4 mg/kg Q2W was chosen for initial burosumab treatment per age group (Cohort 1 and 3, respectively); however, both 0.4 mg/kg and 0.8 mg/kg were intended to be evaluated in this study as a potential starting dose in infants affected by XLH.

Dose escalation by 0.4 mg/kg up to a maximum of 2.0 mg/kg Q2W was possible if clinically not contraindicated.

Objectives and Outcomes/endpoints

Primary and secondary objectives with corresponding endpoints are summarised in Table 6.

Table 6: Primary and Secondary Study Objectives and Endpoints

Primary objective	**Primary endpoint**
To assess the safety and tolerability of burosumab in pediatric subjects with XLH starting treatment below 12 months of age with up to 48 weeks of exposure.	• Incidence, frequency, and severity of AEs and SAEs, including clinically significant changes in laboratory and imaging assessments, from Baseline to scheduled timepoints (measured throughout the study up to Week 48).
Secondary Objectives	**Secondary Endpoints**
To characterize the effect of burosumab on serum phosphate and 1,25$[OH]_2$D in pediatric subjects with XLH starting treatment below 12 months of age.	• Change from Baseline over time (Week 20, 26, 32, 40, and 48) in: ○ Serum phosphate. ○ 1,25$(OH)_2$D.
To characterize the PK of burosumab following SC injection in pediatric subjects below 12 months of age with XLH.	• Burosumab serum concentrations and PK parameters, including CL/F, V/F, AUC, C_{max}, and other parameters, as appropriate, following SC administration
To assess the clinical effects of burosumab on growth and prevention and/or healing of rickets and skeletal deformities.	• Change from Baseline over time and at Week 48 in serum ALP.

	• Change from Baseline in radiographic appearance of rickets severity as assessed by the RGI-C scoring system at Week 48. • Change from Baseline or from time of appearance in rickets severity assessed by total RSS at Week 48. • Change from Baseline in lower extremity skeletal abnormalities, including genu varum and genu valgus, as determined by the RGI-C long leg score at Week 48. • Change from Baseline in recumbent length at Week 48 in cm, height-for-age z-scores, and percentiles.

Sample size

The sample size determination was not based on a statistical power consideration. The study was part of the PIP commitment and was designed to determine the safety profile of burosumab in at least 14 paediatric patients with XLH aged from birth to less than 1 year (0 to <12 months of age) at study entry.

The final number of subjects enrolled in each cohort was also subject to DSMB recommendations and communicated to the Sponsor's Medical Monitor after reviewing all available safety, PD, PK, and (when available) PK/PD relationship data.

Randomisation

The study was uncontrolled.

Blinding (masking)

This was an open-label study.

Statistical methods

Descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and frequency distributions and percentages for discrete variables were utilised.

Results

Participant flow

A total of 16 subjects were enrolled in this study (Table 7).

Table 7: Subject Disposition by Cohort and All (truncated by Assessor)

	Cohort 1 Age ≥6 to <12 months, 0.4 mg/kg starting dose (N=3)	Cohort 2 Age ≥6 to <12 months, 0.8 mg/kg starting dose (N=9)	Cohort 3 Age <6 months, 0.4 mg/kg starting dose (N=4)	All (N=16)
Screened, N	3	9	4	16
Screened but not Enrolled [*]	0	0	0	1
Enrolled [n, (%)]	3 (100)	9 (100)	4 (100)	16 (100)
Enrolled but not treated [a]	0	0	0	0
SAF [a]	3 (100)	9 (100)	4 (100)	16 (100)
FAS [a]	3 (100)	9 (100)	4 (100)	16 (100)
PD Analysis Set [a]	3 (100)	9 (100)	4 (100)	16 (100)
Study completion status [n, (%)] [b]				
Study completion	3 (100)	8 (88.9)	4 (100)	15 (93.8)
Study discontinuation	0	1 (11.1)	0	1 (6.3)

FAS=Full Analysis Set; PD=pharmacodynamic; SAF=Safety Analysis Set

Two subjects were screen failures. One subject was a screen failure but was later rescreened and enrolled. Subjects were assigned to a cohort only after screening process was completed.

One subject (6.3%) discontinued from the study for "other reason", whereas the remaining 15 subjects completed the study. The reason for discontinuing the study was that the subject transitioned into receiving the drug as standard of care at a local hospital due to family difficulties in complying with the schedule.

Recruitment

The study was conducted at 9 study sites in Sweden, Austria, France, UK, Spain, and Italy, of which 8 sites enrolled at least one subject.

Conduct of the study

Protocol deviations

Fifteen subjects (93.8%) had at least 1 protocol deviation, of which 13 subjects (81.3%) had at least 1 key protocol deviation. Of the 226 events that were regarded as protocol deviations, 90 events were key protocol deviations.

The most common key deviations (>20%) were related to, in descending order of incidence: laboratory (75.0%), procedures/tests (62.5%), ICF issues (25.0%), and study drug (25.0%).

Two subjects had protocol deviations due to COVID-19; both were non-key protocol deviations.

Protocol amendments

The original protocol, Version 1.0, dated 23 May 2019, was amended six times. The original protocol (Version 1.0) was submitted to the IEC but not approved. The Protocol Version 2.0 was submitted and approved by the IEC.
The first subjects were enrolled under Protocol Version 3.0 dated 24 SEP 2019. All subsequent

updates to the protocol were amendments to Version 3.0. The current version of the protocol is Version 3.0 Amendment 4 dated 13 Oct 2022. The MAH has provided a comprehensive summary of protocol amendments.

Changes in Version 3.0 Amendment 3, dated 27 Jan 2021, included update of the planned treatment duration from at least 64 weeks to up to 48 weeks since the safety and efficacy of burosumab had previously been demonstrated in other clinical trials included in the marketing authorisation. In addition, a fourth cohort (<6 months, 0.8 mg/kg starting dose) was removed to allow for flexibility for dosing of subjects.
Changes in Version 3.0 Amendment 4, dated 13 October 2022, included a reduction of the minimum number of evaluable subjects to be enrolled into the study from at least 20 to at least 14 in line with the PIP commitment.

Baseline data

Baseline demographic data is presented in Table 8.

No paediatric patients < 4 months of age were dosed with burosumab in Study BUR-CL207. This was partly due to the logistical difficulties of families with very small babies to participate in a clinical trial requiring multiple hospital visits, assessments and blood draws in particular, and by the protocol's requirement of fasting serum phosphate to be below the age-adjusted lower limit of normal. It was observed during the study that patients' mothers also affected by XLH, this being an X-linked genetic disease, were themselves treated with oral phosphate as part of conventional therapy, so phosphate was passed on to their babies via breastfeeding. Once breastfeeding was stopped, the XLH infants' serum phosphate levels indeed dropped to below normal levels, and they became eligible to enter the study.

The mean (SD) levels of serum phosphate in subjects at Baseline was 3.1 (0.38) mg/dL [1 (0.12) mmol/L] (normal range for patients aged from 1 month to < 1 year: 3.6 to 6.7 mg/dL [1.16-2.17 mmol/L]).
The mean (SD) levels of $1,25(OH)_2D$ in subjects at Baseline was 65.21 (37.546) pg/mL (normal range: 19.9 to 79.3 pg/mL).

Fifteen of the 16 subjects (93.8%) had been diagnosed by genetic *PHEX* testing; the remaining subject was diagnosed prenatally.

Six subjects (37.5%) had experienced XLH-related symptoms prior to participating in the study. The mean (SD) number of days from the first XLH symptoms to Baseline was 180.0 (66.24) days (range: 122 to 295 days) and the mean (SD) number of days from XLH diagnosis to Baseline was 147.2 (52.86) days (range: 72 to 212 days) for the six subjects.

Table 8: Demographics by Cohort and All (SAF) (truncated by assessor)

	Cohort 1 Age ≥6 to <12 months, 0.4 mg/kg starting dose (N=3)	Cohort 2 Age ≥6 to <12 months, 0.8 mg/kg starting dose (N=9)	Cohort 3 Age <6 months, 0.4 mg/kg starting dose (N=4)	All (N=16)
Age (weeks old) at Baseline				
n	3	9	4	16
mean (SD)	36.90 (6.300)	39.73 (6.739)	21.28 (2.631)	34.59 (9.753)
min-max	29.7-41.4	29.0-48.0	17.7-23.4	17.7-48.0
Age (weeks old) at XLH diagnosis				
n	1	2	3	6
mean (SD)	1.30 (NA)	12.45 (7.707)	5.73 (5.160)	7.23 (6.466)
min-max	1.3-1.3	7.0-17.9	0.4-10.7	0.4-17.9
missing	2	7	1	10
Sex [n, (%)]				
Male	2 (66.7)	5 (55.6)	2 (50.0)	9 (56.3)
Female	1 (33.3)	4 (44.4)	2 (50.0)	7 (43.8)
Race [n, (%)]				
White	1 (33.3)	9 (100)	4 (100)	14 (87.5)
Black or African American	0	0	0	0
Asian	0	0	0	0
Other/Unknown/ Not Reported	2 (66.7)	0	0	2 (12.5)

Outcomes and estimation

Exposure and dose adjustments

All 16 enrolled subjects received the scheduled burosumab dose at each dosing cycle before the EOT/ET (Week 48), with the exception of three missed doses.

Fifteen of the 16 enrolled subjects received burosumab for 48 weeks. One subject in Cohort 1 was enrolled under Protocol Version 3.0 and hence completed 62 weeks of treatment. The mean (SD) exposure to burosumab was therefore 48.26 (5.181) weeks.

Eleven subjects had at least one dose adjustment during the study, all of which resulted in a dose increase. The mean weight adjusted dose is presented in Table 9.

Table 9: Extent of Exposure by Cohort and All (SAF) (truncated by Assessor)

	Cohort 1 Age ≥6 to <12 months, 0.4 mg/kg starting dose (N=3)	Cohort 2 Age ≥6 to <12 months, 0.8 mg/kg starting dose (N=9)	Cohort 3 Age <6 months, 0.4 mg/kg starting dose (N=4)	All (N=16)
Weight-adjusted average administered dose (mg/kg) [b] [c]				
n	3	9	4	16
mean (SD)	1.117 (0.5573)	0.913 (0.1996)	0.928 (0.3678)	0.955 (0.3102)
median	0.810	0.800	1.045	0.885
Q1, Q3	0.780, 1.760	0.790, 1.100	0.680, 1.175	0.785, 1.135
min-max	0.78-1.76	0.64-1.17	0.40-1.22	0.40-1.76

Pharmacodynamic markers

The pharmacodynamic markers serum phosphate and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) were secondary endpoints in the study. The results are presented in Table 10 (phosphate) and Table 11 ($1,25(OH)_2D$).

Table 10: Serum Phosphate (mg/dL) at Baseline and EOT/ET

Scheduled Visit	Statistics	Cohort 1 (N=3)	Cohort 2 (N=9)	Cohort 3 (N=4)	All (N=16)
Baseline	**Observed**				
	n	3	9	4	16
	Mean (SD)	2.993 (0.3993)	3.027 (0.3854)	3.359 (0.3396)	3.104 (0.3833)
EOT/ET	**Observed**				
	n	3	8	4	15
	Mean (SD)	3.540 (0.9594)	3.727 (0.3806)	3.800 (0.2105)	3.709 (0.4713)
	Change from Baseline				
	n	3	8	4	15
	Mean (SD)	0.547 (0.5618)	0.646 (0.3804)	0.441 (0.2842)	0.572 (0.3781)
	Percentage change from Baseline				
	n	3	8	4	15
	Mean (SD)	16.875 (16.0982)	21.869 (14.1200)	13.743 (9.4988)	18.703 (13.0198)

Serum phosphate level from central laboratory values.

Cohort 1: Aged ≥ 6 to < 12 months, 0.4 mg/kg starting dose; Cohort 2: Aged ≥ 6 to < 12 months, 0.8 mg/kg starting dose; Cohort 3: Aged < 6 months, 0.4 mg/kg starting dose.

EOT/ET=end of treatment/early termination, SD=standard deviation

Table 11: Serum $1,25(OH)_2D$ (pg/mL) at Baseline and EOT/ET

Scheduled Visit	Statistics	Cohort 1 (N=3)	Cohort 2 (N=9)	Cohort 3 (N=4)	All (N=16)
Baseline	**Observed**				
	n	3	9	4	16
	Mean (SD)	66.60 (20.673)	71.39 (46.139)	50.25 (25.918)	65.21 (37.546)
EOT/ET	**Observed**				
	n	3	7	4	14
	Mean (SD)	70.27 (10.228)	70.01 (17.574)	81.38 (20.657)	73.31 (16.885)
	Change from Baseline				
	n	3	7	4	14
	Mean (SD)	3.67 (27.335)	-2.50 (55.026)	31.13 (44.150)	8.43 (46.801)
	Percentage change from Baseline				
	n	3	7	4	14
	Mean (SD)	13.83 (40.748)	29.60 (78.850)	152.05 (260.111)	61.20 (149.444)

Cohort 1: Aged ≥ 6 to < 12 months, 0.4 mg/kg starting dose; Cohort 2: Aged ≥ 6 to < 12 months, 0.8 mg/kg starting dose; Cohort 3: Age < 6 months, 0.4 mg/kg starting dose.
1,25(OH)2D=1,25-dihydroxyvitamin D, EOT/ET=end of treatment/early termination, SD=standard deviation
The normal range of serum 1,25(OH)2D of central laboratory was 19.9 to 79.3 pg/mL

All post-Baseline mean serum phosphate levels were greater than those at Baseline and at EOT/ET the mean phosphate levels were all within the age-adjusted normal ranges.

Moderate increases in mean serum $1,25(OH)_2D$ concentrations were observed, followed by a gradual decrease, suggesting that the regulation and metabolism of $1,25(OH)_2D$ adjusted to the correction of phosphate homeostasis with burosumab treatment

Other secondary efficacy endpoints

Serum Alkaline Phosphatase (ALP)

The normal range for ALP varied by gender and age: in females, the normal ALP range was 48 to 406 U/L for the age group of 0 to 1 month and 124 to 341 U/L for 1 month to < 1 year; in males, the normal ALP range was 75 to 316 U/L for the age group of 0 to 1 month and 82 to 383 U/L for 1 month to < 1 year.

The mean (SD) serum ALP concentration was 713.7 (119.30) U/L at Baseline (n=16).

Decreases in mean (SD) serum ALP concentrations were observed at Week 4 (558.3 [133.66] U/L; mean percentage change: -22.4%) (n=12). Further decreases were observed over time and lowered ALP levels were sustained through the treatment period: mean percentage changes from Baseline to Weeks 8, 12, 20 and EOT/ET were -16.1% (n=15), -17.6% (n=14), -30.9% (n=15) and -29.5% (n=15), respectively. At follow-up/EOS (n=14), the mean (SD) serum ALP value was 386.9 (105.37) U/L, with a mean (SD) decrease from Baseline of 325.1 (104.65) U/L (45.5%). Cohorts 2 and 3 demonstrated similar decreasing patterns in serum ALP that were comparable to the overall subject population, whereas an increase in mean serum ALP was observed at EOT/ET for Cohort 1. However, Cohort 1 was the first cohort and included three subjects treated with a lower burosumab starting dose of 0.4 mg/kg. In addition, one of the three subjects was severely affected by XLH and despite receiving dose increases up to 2.0 mg/kg, their XLH biochemistry data did not improve; though, radiological improvements of rickets were noted at Week 40 compared to Baseline.

Radiographic Global Impression of Change Score (RGI-C) and Total Rickets Severity Score (RSS)

Radiographs were independently evaluated by three radiographers according to the RGI-C scale. The three radiographers reviewed the X-rays in parallel without knowledge of the assessments of the other readers, they were not provided with any subject demographics, such as Site ID, Subject ID and procedure date and did not view any assessments performed by the site Investigators. X-ray images of the bilateral AP knee, bilateral PA hand/wrist and bilateral standing long leg (if available) were reviewed and graded according to the RGI-C scale, metaphyseal abnormalities scored, and tibia/fibula alignment deformities evaluated. A single radiographer evaluated bilateral AP knee and bilateral PA hand/wrist X-rays and provided a grade according to the RSS scale.

Rickets becomes apparent when children start walking, with the onset of weight bearing; therefore, due to the age of the patient population (< 1 year of age), there was no required minimum rickets score for study entry, as rickets may not have yet manifested prior to Screening. Subjects' RGI-C scores and RSSs were documented throughout the study in order to evaluate these endpoints; however, these scores have never been evaluated in paediatrics < 1 year of age, and a clinically meaningful interpretation of "change from Baseline" in this young patient population may be impaired when signs of rickets have not yet developed by study entry. Therefore, also due to the small sample size, meaningful conclusions cannot be drawn. Efficacy endpoints pertaining to RGI-C scores and RSSs are therefore not presented here.

Growth Velocity

Growth velocity was assessed by recumbent length and height-for-age z-score.

The overall mean (SD) recumbent length was 67.06 (4.358) cm (n=16) at Baseline. At EOT/ET, the mean recumbent length was 78.43 (3.081) cm (n=14), with an increase of 11.86 (2.107) cm and a percentage change of 18.0%.

The mean (SD) height-for-age z-scores were -1.14 (1.194) (n=16) at Baseline and -1.51 (0.892) (n=14) at EOT/ET, with a mean (SD) change of -0.13 (0.752).

2.4.2. Discussion on clinical efficacy

The current indication for Crysvita in XLH is: CRYSVITA is indicated for the treatment of X-linked hypophosphataemia, in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.

The updated indication as claimed by the MAH is: CRYSVITA is indicated for the treatment of X-linked hypophosphataemia in infants from 1 month to 1 year of age with hypophosphatemia (see section 5.1), in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.

Design and conduct of clinical studies

Study BUR-CL207 was initially submitted in accordance with Article 46 of Regulation (EC) No1901/2006 in procedure CRYSVITA EMEA/H/C/004275/P46/009. As the current variation was flagged in the p46 procedure, the study was only synoptically assessed in the previous procedure. Some comments on issues to be addressed in the current procedure was however given.

Study BUR-CL207 was a multicentre, open-label trial in paediatric patients from birth to < 1 year of age with XLH conducted in six European countries. All enrolled subjects received burosumab. The study comprised a total treatment period of up to 48 weeks.

The MAH did not discuss the rational for the uncontrolled study design. This constrained the assessment of efficacy and safety. Since the study is included in the PIP, it is expected that this has been addressed as part of the PIP and . is not further pursued. The study is completed and the exact reason(s) for running an uncontrolled study is also less relevant at this time point.

Eligibility criteria included age <12 months at burosumab treatment initiation, a diagnosed PHEX mutation or variant of uncertain significance in either the subject or a directly related family member with appropriate X-linked inheritance, and serum phosphate levels below the age-specific lower limit of normal (LLN) at screening. This was considered adequate.

In total, the study enrolled 16 subjects. The sample size determination was not based on a statistical power consideration. The study was part of the PIP commitment, and the agreed sample size was at least 14 paediatric patients with XLH aged from birth to less than 1 year (0 to <12 months of age) at study entry. This was fulfilled and thereby accepted. The resulting study population is nevertheless very limited.

The study population comprised of three cohorts based on age and starting dose: cohort 1 (6–12 months, starting dose 0.4 mg/kg; n=3), cohort 2 (6–12 months, starting dose 0.8 mg/kg; n=9) and cohort 3 (0-<6 months, starting dose 0.4 mg/kg; n=4). No subject below the age of 4 months was enrolled in the study.

The primary objective of Study BUR-CL207 was safety. Secondary objectives included pharmacodynamic (PD) markers and selected efficacy parameters. Objectives and endpoints were agreed in the PIP.

The number of subjects with at least one key protocol deviation was high, 13/15 subjects (81%). Moreover, these thirteen subjects reported in total 90 events of key protocol deviations. The MAH has clarified that the majority of the key protocol deviations pertained to the inability to perform certain laboratory tests (56%) or study procedures deviations (24%) due to the young age of the subjects and their low blood volumes, and with the study being performed during the COVID-19 pandemic. This was acknowledged. From the full list of protocol deviations, collection of serum phosphate seems to have been a priority when full blood samples could not be achieved. The impact on primary outcome is therefore not considered to be significantly impacted, despite the high number of protocol deviations.

The original protocol dated 23 May 2019 was amended six times, of which four times after patient inclusion. The protocol amendments are not expected to have had any impact on outcome in this uncontrolled, open label study with descriptive efficacy data only.

In summary, Study BUR-CL207 was performed in accordance with the agreement in the PIP. Nevertheless, the study population is very limited, and all data is derived from a single, open label uncontrolled study. In particular, only four subjects under six months were included, and none of these were under four months of age. The data from the study is not considered to single-handedly support extension of the indication to subjects < 12 months of age with XLH. The possibility of extrapolating efficacy data from the approved paediatric population is discussed below.

Efficacy data and additional analyses

Sixteen subjects were enrolled in the study. In total, 94% (15/16) of the subjects completed the study. The last subject discontinued from the study and transitioned onto receiving the drug as standard of care at a local hospital due to family difficulties in complying with the schedule.

The mean age at baseline in the overall population was 34.6 weeks and in Cohort 3 (< 6 months) 21.3 weeks. The lowest age at baseline was 17.7 weeks.
The median age at XLH diagnosis in the study was 6.5 weeks (n=6 with available data). The age at XLH diagnosis obviously impacts the age at study enrolment. In addition, the MAH has explained that one of the reasons for not enrolling subjects under the age of four months was that phosphate was passed on via breastfeeding from mothers with XLH treated with phosphate substitution, thereby keeping serum phosphate levels over the LLN. Furthermore, the logistical difficulties of families with very small babies to participate in a clinical trial requiring multiple hospital visits, assessments and blood draws may have had impact on the possibility of recruiting younger subjects. While this is understood, the support for a safe and effective treatment of children below the age of six months is very limited. Six subjects had experienced XLH-related symptoms prior to participating in the study. Collection of the nature of existing XLH symptoms was not part of the study protocol. Therefore, only in one subject the symptoms were described. This subject notably exhibited several classical XLH symptoms (Widened/thickened wrist, rachitic rosary, abnormal chest, genu varum, bowing) at the age of six weeks.

There was no primary efficacy endpoint in Study BUR-CL207. Secondary pharmacodynamic endpoints were change from baseline in serum phosphate and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).

In all cohorts, mean serum phosphate increased from levels below to within the normal interval for age (3.6 to 6.7 mg/dL [1.16-2.17 mmol/L]) during burosumab treatment. This is considered to support a beneficial treatment effect in the very limited study population.
Of note, for blood samples to be used for analysis of designated safety/PD parameters, fasting for a minimum of 4 hours was recommended prior to each blood draw. Considering young age of the study population and potential challenges in full time length fasting, blood sampling and inclusion of laboratory results without full length fasting were however not precluded in the analysis. The duration of fasting and fasting conditions (the time of sample collection, the time and type of the last meal or drink) were recorded on the subject's eCRF, according to the CSR. The MAH has presented a comprehensive summary of all phosphate samplings from the subjects reporting fasting deviation, including the values where S-phosphate was collected after 4-h fasting as stipulated (not included in AR for the sake of conciseness). It is agreed with the MAH that the fasting deviation had little effect on serum phosphorus levels. For most cases with fasting deviation, the fasting hours are not available. However, when this information was provided, fasting time was ≥3 h in 12/17 occasions. Of note, the majority of fasting deviations were reported in two single subjects.

In the previous procedure (EMEA/H/C/004275/P46/009), it was noted that a mean increase in serum $1,25(OH)_2D$ in the overall population was almost completely driven by Cohort 3 (0-6 months) with an increase of 152 %. In Cohort 1, there was an increase of 14 % and in Cohort 2, there was a decrease in Serum $1,25(OH)_2D$.
The MAH has commented that the study was not designed to assess efficacy, and further, in a small sample size, outliers can skew the mean. For example, one subject in Cohort 1 had very severe XLH and showed no increase in serum phosphate or $1,25(OH)_2D$. Within a sample of three subjects, this data point skews the mean.
It is agreed that the increase in serum $1,25(OH)_2D$ in the overall study population is consistent with observations in other studies, but the variation between the cohorts is still unexplained. It is considered probable that the very limited sample sizes in the cohorts have contributed to the inconsistent results, with single subjects skewing the mean. Looking at the change from baseline (CFB) at end of treatment (EOT) in 1,25(OH)2D on subject basis, there is a large variation within all three cohorts (Cohort 1: -31% to 147%, Cohort 2: -62% to 178%, Cohort 3: -9% to 540%). The MAH has discussed the possibility that the large variability in CFB correlates to baseline level of serum 1,25(OH)2D. While there is no clearcut correlation, it can be agreed that subjects with high baseline 1,25(OH)2D tend to have a smaller (or negative) CFB and vice versa. The subject with the highest baseline 1,25(OH)2D value, 183 pg/mL, had the largest negative CFB, -62%, while the subject with the lowest baseline 1,25(OH)2D value, 17 pg/mL, reported a CFB of 540%. In study UX023-CL301 in subjects 1-12 years of age, serum 1,25(OH)2D CFB to Week 40 varied from -44% to 304%, supporting that this large variation in serum 1,25(OH)2D in Study BUR-CL207 is not specific for infants. This issue is therefore not further pursued.

Efficacy parameters included Radiographic Global Impression of Change Score (RGI-C), Total Rickets Severity Score (RSS) and growth velocity. The MAH has explained that rickets becoming apparent only when children start walking, with the onset of weight bearing. Subjects' RGI-C scores and RSSs were documented throughout the study in order to evaluate these endpoints; however, these scores have never been evaluated in paediatrics < 1 year of age, and a clinically meaningful interpretation of "change from baseline" in this young patient population may be impaired when signs of rickets have not yet developed by study entry. Therefore, also due to the small sample size, meaningful conclusions could not be drawn. This is endorsed.
The mean height-for-age z-scores in the study population decreased during treatment. The large

inter-individual variation in growth in combination with the very limited study population hampers meaningful interpretation.

As concluded above, an extension of the indication to subjects below one year of age thus requires extrapolation of efficacy from the approved paediatric population. XLH is caused by mutations to the PHEX gene, in turn leading to excessive amounts of circulating FGF23. The genetic mechanism is inborn and thus independent of age.
Burosumab is a monoclonal antibody that binds to and inhibits the excess biological activity of FGF23. This is also anticipated to be independent of age. This is supported by the observation in the trial that serum phosphate increased to normal levels with burosumab treatment in all three cohorts.
In the approved paediatric population, the increase in serum phosphate was shown to translate into a positive effect on rickets as assessed by e.g., RGI-C and RSS. It is considered reasonable that this observation could be extrapolated also to younger children.
In summary, based on the common pathophysiological mechanism for XLH and mechanism of action of burosumab over all ages, it is possible that a beneficial effect of burosumab could be extrapolated from the approved populations to younger children. The MAH has presented data from clinical and preclinical studies indicating that phosphate-regulating mechanisms are functionally mature and highly active in early infancy:

- In healthy infants under 6 months, renal tubular reabsorption of phosphate exceeds that of older children and adults (Bistarakis, 1986), consistent with the higher normal serum phosphate levels observed during this developmental period. In animal models, expression of the sodium-phosphate cotransporter NaPi-2 in the renal cortex is approximately two-fold greater in young compared with adult kidneys (Silverstein, 1996), confirming that the renal phosphate transport system is already well developed and physiologically active.
- The infant growth plate is highly active, with accelerated phosphate incorporation and chondrocyte hypertrophy compared with older children (Rauch, 2001). Serum alkaline phosphatase and parathyroid hormone levels are naturally elevated in infancy but within developmental norms and do not impede the response to phosphate repletion (Misra, 2008). These features indicate that burosumab's FGF23 blockade targets a physiologically responsive skeletal system rather than an immature one.
- Vitamin D metabolism and intestinal mineral handling are robust in early infancy. Conversion of 25(OH)D to calcitriol is efficient in infants as young as one to two months, leading to higher circulating calcitriol concentrations than in older children and adults (Greer, 1989). Intestinal calcium and phosphate absorption is already effective by four weeks of age and increases proportionally with calcitriol levels (Kovacs, 2014; Senterre, 1982).

The MAH concluded that, collectively, these findings demonstrate that renal, skeletal and intestinal pathways relevant to burosumab's mechanism of action are physiologically mature in early infancy.

To further substantiate the physiological basis for extrapolating efficacy and safety in infants, the MAH sought input from two leading international experts in paediatric phosphate/calcium metabolism and XLH. The experts declared interests with pharmaceutical companies. Both experts emphasised that renal phosphate handling in infants is intact and highly avid, consistent with the literature cited above, and that no evidence exists of functional renal immaturity that would reduce burosumab efficacy. One expert highlighted that fractional tubular reabsorption of phosphate is higher in infants than in older children, while the other noted that elevated 1,25-dihydroxyvitamin D levels in infancy reflect normal growth demands rather than immaturity of renal hydroxylation.

Taken together, it is considered that sufficient support for extrapolation of the effect from children >12 months of age to subjects aged from 6 months to 1 year is provided. However, a lower starting dose and a more conservative dose titration is proposed for this age cohort (please refer to Clinical pharmacology).
The experience of burosumab treatment in subjects from 1 month to six months in Study BUR-CL207 is very limited (n=4; all over the age of 4 months). Notwithstanding, the MAH presented support for that the renal phosphate handling in infants is intact from early age from the literature and from statements by the two clinical experts. While the level of proof is weaker for the lowest age cohort, the MAH's argumentation supporting extrapolation of efficacy data from older children also to this age cohort is accepted. The proposed posology for this age cohort is agreed.

In the marketing authorisation procedure for the initial paediatric population (EMEA/H/C/4275), only children with radiological evidence of bone disease had been included in the clinical studies. It was concluded that efficacy could not be extrapolated to subjects without radiological evidence of bone disease. This is reflected in the approved indication. However, as mentioned above, radiographical evidence of bone disease may not be present in young children, not below the age of 6 months since rickets mainly develops with the onset of weight bearing. The MAH argued that the aim of early treatment is to prevent or delay the onset of rickets and skeletal deformities by restoring phosphate homeostasis before radiographic disease becomes apparent. The MAH highlighted that biochemical consequences of XLH precede the onset of skeletal changes evident through imaging. For example, rachitic skeletal deformities usually become apparent around 6 months of age, while by 3 months of age, the classic biochemical profile with hypophosphatemia and increasing ALP is present in most infants with XLH. The benefit of starting treatment early to avoid irreversible skeletal changes is acknowledged.

The possibility for a skeletal deviation to be reversible at different ages has not been discussed by the MAH, but it is anticipated that it would be hard to establish an age below which such deviations are always reversible. Therefore, the MAH's proposal to omit the requirement for radiographic evidence of XLH in subjects below the age of 1 year is supported. Instead, the MAH proposed to include hypophosphataemia in the indication for this age cohort. This was agreed. Section 4.2 has been amended with a wording reflecting that treatment should not be started unless serum phosphate is below the lower limit of normal for age.

Dosing

From an efficacy point of view, with a long-term treatment goal and dose titration based on serum phosphate, it is not considered crucial to have a high starting dose. The choice of starting dose from a safety perspective is further discussed below.

The approved starting dose in the paediatric population >12 months is 0.8 mg/kg with possibility to dose titrate with increments of 0.4 mg/kg every 4 weeks up to a maximum dose of 2 mg/kg or 90 mg, based on fasting serum phosphate two weeks after dose. For safety reasons, the first cohort in Study BUR-CL207 used a starting dose of 0.4 mg/kg. The youngest age cohort also used the lower starting dose.

Eleven subjects had a dose adjustment during the study, of which 10 were dose increases. The median dose in the study was 0.88 mg/kg. The highest median dose, 1.04 mg/kg, was reported in Cohort 3 (age <6 months). Of note, at least one subject in Cohort 3 seems to have stayed on the starting dose 0.4 mg/kg. The observed and simulated burosumab dose-exposure is discussed in the Clinical Pharmacology section. In summary, the proposed starting dose for subjects from 1 to 6 months is 0.4 mg/kg with possibility to dose titrate up to a maximum of 0.8 mg/kg based on fasting serum phosphate two weeks after dose. This is agreed. In the US, Crysvita is indicated for

treatment of XLH from 6 months of age. The recommended starting dose is 1 mg/kg for patients weighing <10 kg and 0.8 mg/kg for patients weighing ≥10 kg. The MAH summarised data from the literature, from an American registry study and from Study BUR-CL207. The reported starting doses begin at 0.8 mg/kg with a maximum dose of 2 mg/kg. The experience in children 6-<12 months is overall very limited, but there are no reports of hyperphosphataemia in the summary. To further mitigate the risk of hyperphosphataemia, the MAH accepted to extend the monitoring of fasting serum phosphate after treatment initiation and dose adjustment for all infants < 12 months of age. This further ensures an appropriate treatment. Hence, the proposed starting dose, dose increment, and frequency of up-titration in paediatric patients aged ≥6 to <12 months are considered acceptable.

2.4.3. Conclusions on the clinical efficacy

The Study BUR-CL207 study population is limited, and all data is derived from a single, open label uncontrolled study. In particular, only four subjects under six months were included, and none of these were under four months of age.

The data from the study is not considered to single-handedly support extension of the indication to subjects < 12 months of age with XLH. However, a positive treatment effect on serum phosphate was seen in both age cohorts. The MAH has presented support from the literature and from statements by two clinical experts for that the renal phosphate handling in infants is intact from early age. The MAH's argumentation supporting extrapolation of the effect from children >12 months of age to subjects aged from 1 month to 1 year is considered acceptable.

The benefit of starting treatment early to avoid irreversible skeletal changes is acknowledged. The MAH's proposal to omit the requirement for radiographic evidence of XLH in subjects below the age of 1 year provided hypophosphatemia is supported.

2.5. Clinical safety

Introduction

Safety of burosumab in the approved paediatric population (≥ 1 – 17 years) is summarised below.

As per the currently approved SmPC for burosumab, the most common adverse drug reactions (> 10%) reported in paediatric patients with XLH during clinical trials, based on completed long term studies up to a maximum exposure to burosumab of 214 weeks (with variable period of exposure across the safety population), were Cough (55%), injection site reactions[1] (54%), Pyrexia (50%), Headache (48%), Vomiting (46%), Pain in extremity (42%), Tooth abscess (40%), Vitamin D decreased (28%), Diarrhoea (27%), Nausea (21%), Rash (20%), Constipation (12%) and Dental caries (11%).

Patient exposure

The safety analysis set includes all subjects (N=16) who received at least one dose of burosumab in the Phase 1/2 Study BUR-CL207.

[1] 'Injection site reactions' includes the following PTs: Injection site reaction, Injection site erythema, Injection site pruritus, Injection site swelling, Injection site pain, Injection site rash, Injection site bruising, Injection site discolouration, Injection site discomfort, Injection site haematoma, Injection site haemorrhage, Injection site induration, Injection site macule and Injection site urticaria.

The mean (SD) duration of subject participation in the study was 59.2 (6.66) weeks from the date of informed consent to study completion or discontinuation, and 56.2 (7.42) weeks from the first dose to study completion or discontinuation.
The mean (SD) exposure to burosumab was 48.26 (5.181) weeks for all subjects and the total subject-weeks exposure to burosumab was 772.14 weeks. The mean (SD) number of dosing cycles (every 2 weeks) was 26.1 (5.99). For Cohorts 1, 2 and 3, the mean (SD) weight adjusted average administered doses were 1.117 (0.5573), 0.913 (0.1996) and 0.928 (0.3678) mg/kg, respectively.

Eleven subjects had at least one dose adjustment (all of which were dose increases) during the study; the main reason for dose adjustment was change in fasting serum phosphate level (eight subjects; 72.7%).

Adverse events

All subjects in Study BUR-CL207 experienced treatment-emergent adverse events (TEAEs) (Table 12).

A total of six study drug-related TEAEs (Blood parathyroid hormone increased [n=4], Craniosynostosis [n=1] and Dermatitis acneiform [n=1]) were reported in four subjects (25.0%; one subject in Cohort 1 and three subjects in Cohort 2). Three events were reported as mild and one as severe.

Table 12: Adverse Events: Summary Table by Cohort and All (SAF) (truncated by Assessor)

Category	Cohort 1 Age ≥6 to <12 months, 0.4 mg/kg starting dose (N=3)	Cohort 2 Age≥6 to <12 months, 0.8 mg/kg starting dose (N=9)	Cohort 3 Age <6 months, 0.4 mg/kg starting dose (N=4)	All (N=16)
Pre-existing conditions [n, (%)]	0	5 (55.6)	2 (50.0)	7 (43.8)
TEAEs [n, (%)]	3 (100)	9 (100)	4 (100)	16 (100)
By severity (NCI CTCAE Version 5.0) [n, (%)] [a]				
Mild (Grade 1)	0	4 (44.4)	1 (25.0)	5 (31.3)
Moderate (Grade 2)	3 (100)	4 (44.4)	3 (75.0)	10 (62.5)
Severe (Grade 3)	0	1 (11.1)	0	1 (6.3)
Life threatening (Grade 4)	0	0	0	0
Death (Grade 5)	0	0	0	0
Treatment-emergent AESI [n, (%)]	3 (100)	5 (55.6)	1 (25.0)	9 (56.3)
By AESI [n, (%)]				
Ectopic mineralization	1 (33.3)	0	0	1 (6.3)
Hyperparathyroidism	1 (33.3)	3 (33.3)	0	4 (25.0)
Hypersensitivity	1 (33.3)	3 (33.3)	1 (25.0)	5 (31.3)
Injection site reaction	1 (33.3)	0	0	1 (6.3)
Unclassified	1 (33.3)	1 (11.1)	0	2 (12.5)
TEAEs leading to permanent discontinuation of study treatment or study [n, (%)]	0	0	0	0
Any treatment-emergent SAE including sudden or unexplained death [n, (%)]	1 (33.3)	1 (11.1)	0	2 (12.5)
Treatment-emergent SAE leading to death [n, (%)]	0	0	0	0
Any related treatment-emergent SAE including death [n, (%)]	0	1 (11.1)	0	1 (6.3)

AESI=adverse events of special interest; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PT=preferred term; SAE=serious adverse event; SAF=Safety Analysis Set; SOC=system organ class; TEAE=treatment-emergent adverse event; %=n/N x 100 unless the denominator for percentage calculation is specified.
1) Subjects with multiple events are counted only once per SOC and PT.

A summary of all TEAEs in Study BUR-CL207, by SOC and PT, reported in ≥ 3 subjects is presented in Table 13.

Table 13: TEAEs in Study BUR-CL207, by SOC and PT, Occurring in ≥ 3 Subjects by Cohort (SAF)

	Cohort 1 Age ≥ 6 to < 12 months, 0.4 mg/kg starting dose (N=3)	Cohort 2 Age ≥ 6 to < 12 months, 0.8 mg/kg starting dose (N=9)	Cohort 3 Age < 6 months, 0.4 mg/kg starting dose (N=4)	All (N=16)
Subjects with at least one TEAE [n (%)]	3 (100)	9 (100)	4 (100)	16 (100)
Infections and infestations	3 (100)	9 (100)	3 (75.0)	15 (93.8)
Nasopharyngitis	0	4 (44.4)	3 (75.0)	7 (43.8)
Rhinitis	1 (33.3)	3 (33.3)	3 (75.0)	7 (43.8)
Upper respiratory tract infection	1 (33.3)	5 (55.6)	0	6 (37.5)
COVID-19	0	4 (44.4)	1 (25.0)	5 (31.3)
Bronchiolitis	1 (33.3)	0	2 (50.0)	3 (18.8)
Varicella	1 (33.3)	2 (22.2)	0	3 (18.8)
General disorders and administration site conditions	3 (100)	6 (66.7)	3 (75.0)	12 (75.0)
Pyrexia	3 (100)	6 (66.7)	3 (75.0)	12 (75.0)
Gastrointestinal disorders	2 (66.7)	6 (66.7)	1 (25.0)	9 (56.3)
Constipation	0	3 (33.3)	1 (25.0)	4 (25.0)
Vomiting	2 (66.7)	1 (11.1)	0	3 (18.8)
Investigations	1 (33.3)	6 (66.7)	1 (25.0)	8 (50.0)
Blood parathyroid hormone increased	1 (33.3)	3 (33.3)	0	4 (25.0)
Vitamin D decreased	0	4 (44.4)	0	4 (25.0)
Respiratory, thoracic and mediastinal disorders	2 (66.7)	2 (22.2)	2 (50.0)	6 (37.5)
Cough	1 (33.3)	2 (22.2)	1 (25.0)	4 (25.0)

Notes:
1) Subjects with multiple conditions were counted only once per SOC and PT.
AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, SAF=Safety Analysis Set, SOC=system organ class, TEAE=treatment-emergent adverse event, %=n/N x 100 unless the denominator for percentage calculation is specified

Serious adverse event/deaths/other significant events

Deaths

There were no subject deaths in Study BUR-CL207.

Other Serious Adverse Events (SAE)

Two subjects experienced a total of two treatment-emergent SAEs; one subject from Cohort 1 reported the SAE of Joint dislocation, which was considered by the Investigator to be unrelated to the study drug and one subject from Cohort 2 reported the SAE of Craniosynostosis, which was considered related to the study drug by the Investigator but unrelated by the MAH.

- **Craniosynostosis**

A male paediatric subject enrolled into Cohort 2 of Study BUR CL207 received the first dose of burosumab (0.8 mg/kg body weight) on Day 1. Eleven days after the last burosumab injection, the

subject experienced the SAE of Craniosynostosis (Grade 3) and was hospitalised. The event was reported to be secondary to hypophosphataemia. Craniosynostosis with decreased growth of the head circumference and fusion of two coronal sutures and sagittal suture were noted. The event was resolved following a surgery. No action was taken with burosumab due to the event.

The Investigator considered the event of craniosynostosis to be related to burosumab based on the temporal association and because a causality could not be completely excluded; however, the Investigator noted that due to the severity of XLH in this subject, the process of craniosynostosis may have started prior to initiation of burosumab. The MAH considered the event unrelated due to lack of a biologically plausible mechanism and the observation that craniosynostosis is one of the known possible symptoms of XLH in infants.

- **Joint dislocation**

A female paediatric subject enrolled into Cohort 1 of Study BUR CL207 received the first dose of burosumab (0.4 mg/kg body weight) on Day 1. Five days after the last burosumab injection, the subject had a planned hospitalisation due to a pre-existing condition PT: Joint dislocation. The subject received supportive care. No action was taken with burosumab due to the event. On Day 113, the TEAE of Joint dislocation resolved.

The Investigator and the MAH considered the event of Joint dislocation unrelated to burosumab as it was noted prior to burosumab administration.

Adverse events of special interest (AESI)

AESI reported in the study are summarised in Table 14.

Table 14: Treatment-Emergent AESIs by Cohort and All (SAF)

	Cohort 1 Age ≥6 to <12 months, 0.4 mg/kg starting dose (N=3)	Cohort 2 Age ≥6 to <12 months, 0.8 mg/kg starting dose (N=9)	Cohort 3 Age <6 months, 0.4 mg/kg starting dose (N=4)	All (N=16)
Subjects with at least one Treatment-emergent AESI [n, (%)]	3 (100)	5 (55.6)	1 (25.0)	9 (56.3)
Hypersensitivity [a]	1 (33.3)	3 (60.0)	1 (100)	5 (55.6)
Dermatitis acneiform	0	1 (20.0)	0	1 (11.1)
Drug hypersensitivity	0	1 (20.0)	0	1 (11.1)
Eczema	0	0	1 (100)	1 (11.1)
Hypersensitivity	1 (33.3)	0	0	1 (11.1)
Rash	1 (33.3)	0	0	1 (11.1)
Rash erythematous	0	1 (20.0)	0	1 (11.1)
Swelling face	1 (33.3)	0	0	1 (11.1)
Hyperparathyroidism [a]	1 (33.3)	3 (60.0)	0	4 (44.4)
Blood parathyroid hormone increased	1 (33.3)	3 (60.0)	0	4 (44.4)
Unclassified [a]	1 (33.3)	1 (20.0)	0	2 (22.2)
Eczema asteatotic	1 (33.3)	0	0	1 (11.1)
Vitamin D decreased	0	1 (20.0)	0	1 (11.1)
Ectopic mineralization [a]	1 (33.3)	0	0	1 (11.1)
Nephrocalcinosis	1 (33.3)	0	0	1 (11.1)
Injection site reaction [a]	1 (33.3)	0	0	1 (11.1)
Injection site pain	1 (33.3)	0	0	1 (11.1)

ADA=anti-drug antibodies; AESI=adverse event of special interest; PT=preferred term; SAF=Safety Analysis Set; SOC=system organ class; %=n/N x 100 unless the denominator for percentage calculation is specified.
AESIs were coded with Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or higher.
[a] Denominator=number of subjects with at least one treatment-emergent AESI.
Note:
1) Subjects with multiple events were counted only once per SOC and PT.
2) Subject 102-002 was negative for ADA at Screening (Baseline) since the result of the confirmatory test was negative for this timepoint. Due to positive ADA testing post-treatment, a TEAE of antibody test positive should have been logged for this subject.

Injection Site Reactions

Burosumab is administered by subcutaneous injection, and as such, there is an inherent risk for injection site reactions. One subject in Study BUR-CL207 (Cohort 1) experienced the AESI of Injection site pain (non-serious; Grade 2); the AESI was considered resolved on the same day as onset and no action was taken with burosumab. The AESI occurred 9 days after the previous burosumab injection and on the same day that the subject received other vaccines; therefore, the Investigator considered the event to be unrelated to burosumab.

Hypersensitivity Reactions

Burosumab is a fully human monoclonal antibody, which is generally considered less immunogenic than other protein therapeutics such as murine, chimeric and humanised monoclonal antibodies. However, as humans are diverse in genotype and phenotype, and immunoglobulin G allotypes differ within and between populations, some immune reactions are anticipated (Nelson, 2010). Therefore, hypersensitivity may be associated with burosumab. However, no severe systemic hypersensitivity reactions have been observed in any clinical trials with burosumab.

In clinical trials in children aged > 1 year, when present, any hypersensitivity reactions appeared to be mild/moderate in severity and were mostly rash-related events, which resolved relatively quickly with non-prescription medication and tended not to recur with subsequent burosumab injections.

In Study BUR-CL207, five subjects (one in Cohort 1, three in Cohort 2 and one in Cohort 3) experienced a total of seven hypersensitivity reactions: Dermatitis acneiform, Drug hypersensitivity, Eczema, Hypersensitivity, Rash, Rash erythematous and Swelling face (each reported singly). All reported hypersensitivity reactions were non-serious and were Grade 1 or 2 in severity. The event of Dermatitis acneiform was considered related to burosumab by the Investigator; the remaining events were considered unrelated to burosumab.

Immunogenicity (Presence of Anti-drug Antibodies)

Administration of therapeutic proteins, including recombinant monoclonal antibodies, can elicit an immune response and lead to the production of ADAs. The incidence of ADA positivity (subjects who were negative at baseline and had at least one ADA positive sample post-dose and subjects who had a positive sample at baseline and had a boosted ADA response) in paediatric subjects who were administered burosumab, based on data from clinical studies was 10%; the incidence of neutralising ADAs in paediatric subjects was 3%. Overall, burosumab presents with a low risk of development of ADAs with a low risk of sequelae.

A review of the paediatric and adult subjects who experienced injection site reactions or hypersensitivity reactions showed a wide variation in the time of event onset from initiation of burosumab treatment, and no clear relationship with ADA status was identified. There were also no clinically relevant differences observed in the nature and severity of injection site reactions or

hypersensitivity reactions in ADA-positive subjects when compared to the ADA-negative subjects. Overall, there was no evidence that immunogenicity has an impact on injection site reactions or hypersensitivity adverse events.

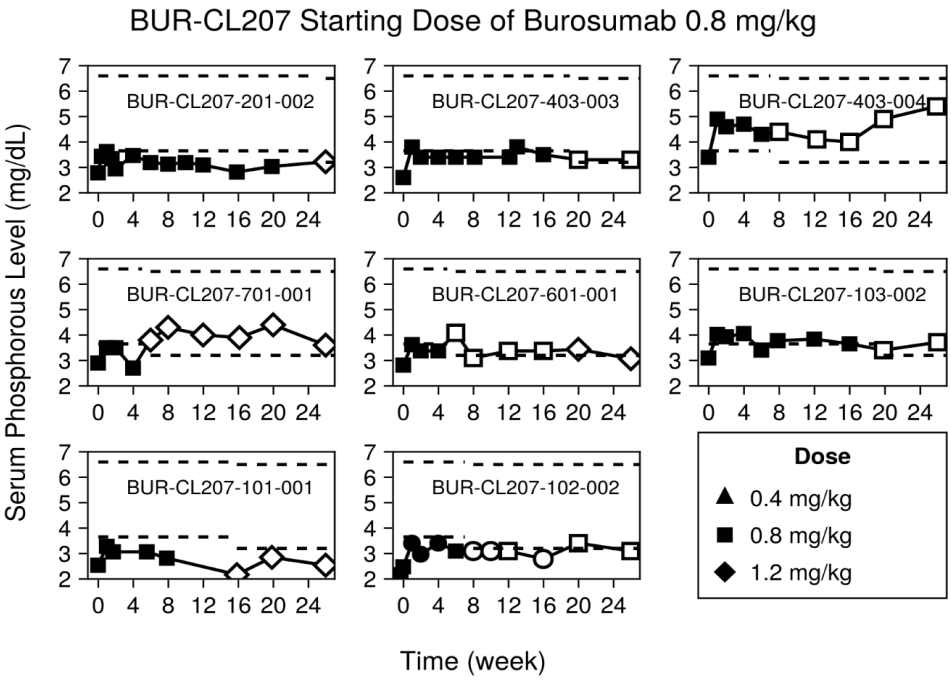
One subject in Cohort 2 of Study BUR-CL207 reported the immunogenicity event of Antibody test positive (non-serious). The subject was ADA negative during the screening period but was ADA positive at all post-baseline visits. No AESIs of hypersensitivity or injection site reactions were reported while the subject was ADA positive.

Hyperphosphataemia

Burosumab treatment increased fasting serum phosphate levels, reaching levels within the age-adjusted normal range at end of treatment in Study BUR-CL207. There were no subjects with TEAEs of Hyperphosphataemia in the study.

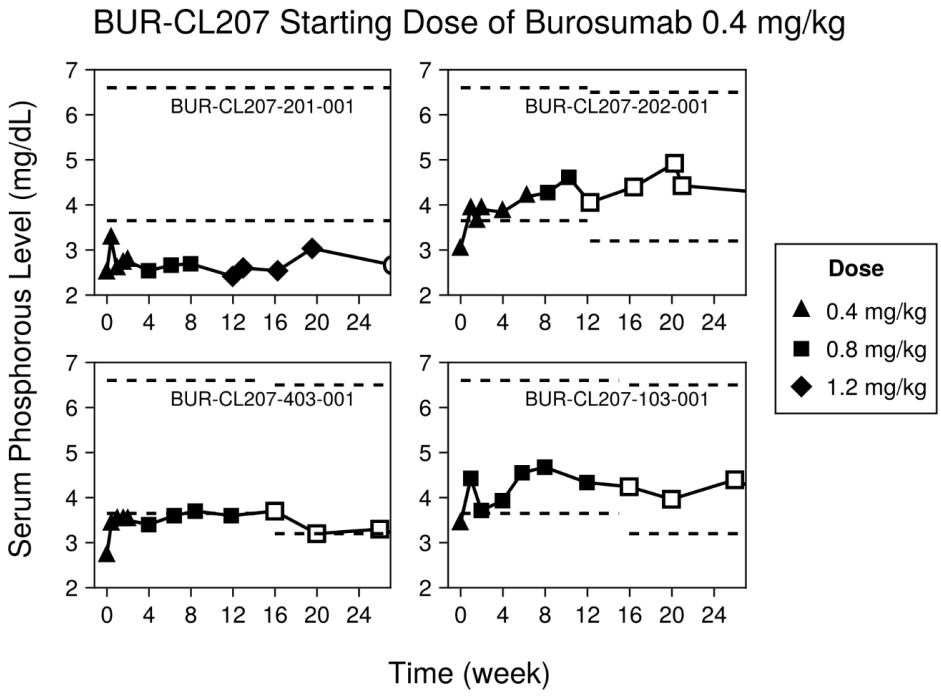
As further support, the MAH has provided data on serum phosphate for all subjects in the study separately (Figure 5, Figure 6).

Figure 5: BUR-CL207 Serum Phosphorus versus Time in Participants Administered Starting Doses of Burosumab 0.8 mg/kg Q2W



Note: dashed lines represent age adjusted serum phosphorus ULN and LLN, symbols represent the dose administered; dark symbol fill represents when participant < 12 months of age, and clear symbols represent when participants are > 12 months of age.
Ref: ~/04_Docs/Report/Figs_Tabs/EMA_03_CL207_spgat_bystart_dot8.png

Figure 6: Serum Phosphorus versus Time in Participants Administered Starting Doses of Burosumab 0.4 mg/kg Q2W



Note: dashed lines represent age adjusted serum phosphorus ULN and LLN, symbols represent the dose administered; dark symbol fill represents when participant < 12 months of age, and clear symbols represent when participants are > 12 months of age.

Ectopic Mineralisation

Ectopic mineralisation is a known risk related to XLH and is exacerbated by oral phosphate and/or active vitamin D supplementation. Burosumab does not appear to be associated with progression of cardiac or renal ectopic mineralisation beyond the natural course of pre-existing disease. A risk of ectopic mineralisation cannot be excluded in the context of hyperphosphataemia.

One subject in Cohort 1 of Study BUR-CL207 experienced the TEAE of Nephrocalcinosis (non-serious; Grade 1[2]) on the same day as receiving burosumab. No action was taken with burosumab, and no treatment was reported for the event. The event resolved and was considered unrelated to burosumab by the Investigator.

Increased Serum Intact Parathyroid Hormone Level

Increases in serum PTH have been observed in some XLH patients during treatment with burosumab.

Four subjects (one in Cohort 1 and three in Cohort 2) experienced five TEAEs of Blood parathyroid hormone increased in Study BUR-CL207, all of which were non-serious and Grade 1 in severity. The TEAEs in three subjects were considered related to burosumab by the Investigator; however, some of the subjects had been previously treated with conventional therapy known for its

[2] During procedure EMEA/H/C/004275/P46/009, the European Medicines Agency noted inconsistences in the Study BUR-CL207 EOS CSR, whereby in Table 14.3.5.1 and Listing 16.2.9.5, it was reported in error that all subjects had Grade 0 Nephrocalcinosis, despite there being one subject who had an event of Nephrocalcinosis that was assessed as Grade 1 by the Investigator at end of treatment. In response, the MAH has published an erratum to the CSR with footnotes added to Table 14.3.5.1 and Listing 16.2.9.5 to 1) clarify that the grading for renal ultrasound was completed separately by the Imaging Central Laboratory for evaluating changes in calcification, whereas the Investigator assessed safety, and 2) to clarify the inconsistent description of Nephrocalcinosis grades that was noted by the European Medicines Agency (BUR-CL207 CSR Erratum 01).

consequences on the parathyroid balance and one subject had a pre-existing condition of Blood parathyroid hormone increased. The TEAE in the remaining subject was considered unrelated to burosumab.

Infections

Fifteen subjects (three from Cohort 1, nine from Cohort 2 and three from Cohort 3) experienced a total of 57 TEAEs pertaining to infections, all of which were non-serious. The most frequently reported TEAEs were Nasopharyngitis (n=12), Rhinitis (n=12), Upper respiratory tract infection (n=8), COVID-19 (n=5), Bronchiolitis (n=3), Varicella (n=3) and Gastroenteritis (n=3). All TEAEs were Grade 1 or 2 in severity, and none were considered related to burosumab by the Investigator. Review of this topic did not reveal any new significant safety information, and the findings are in line with the general paediatric population aged > 1 year, without any exacerbation of severity or seriousness.

Craniosynostosis

A post-authorisation measure, EMEA/H/C/004275/LEG/008.1, was submitted on 24 Jun 2024 to address the request from the PRAC Rapporteur to modify the SmPC for Crysvita solution for injection with an amended warning on craniosynostosis and to monitor children on treatment for signs of craniosynostosis. Following this, the MAH submitted a justification to challenge this request as there is more evidence suggestive of a causal relationship of craniosynostosis with the underlying disease (XLH) than a causal relationship with burosumab, and therefore an update to the SmPC would not be helpful in clinical practice for healthcare professionals and may potentially be unfavourable to XLH patients. The justification also included a proposal to strengthen the pharmacovigilance activities related to monitoring of craniosynostosis. The Preliminary Assessment Report (received on 02 August 2024) agreed that the addition of a warning in the SmPC would not be helpful, and the additional measures proposed are considered adequate at this stage to further investigate and manage the risk. The Finalised Approved Assessment Report with the Committee for Medicinal Products for Human Use adoption was received on 19 September 2024, which endorsed the conclusion presented within the Preliminary Assessment Report.

One subject from Cohort 2 experienced a serious TEAE of Craniosynostosis (Grade 3 in severity).

Kidney Health

One subject experienced the non-serious TEAE of Nephrocalcinosis on the same day as receiving burosumab; further information is presented above.

No other TEAEs pertaining to kidney health were identified from Study BUR-CL207.

Laboratory findings

Clinical Laboratory Evaluations

There were no serious TEAEs associated with clinically significant changes in any clinical laboratory parameter.

Serum Calcium

Mean serum calcium was shown to decrease slightly in this study. At Baseline, the mean (SD) serum calcium was 2.5007 (0.08950) mmol/L. It decreased slightly to 2.4683 (0.09290) mmol/L at EOT/ET. A similar trend was observed across the 3 cohorts. Generally, the changes in calcium level were not considered clinically meaningful for most subjects.

Urinary Calcium

For the limited urinary calcium results available, a slight decrease was observed. The result should be interpreted with caution due to the limited sample size.

Intact Parathyroid Hormone

An overall downward trend was observed for mean iPTH, with slight fluctuations at several visits. The mean (SD) iPTH was 72.49 (36.082) pg/mL at Baseline and 44.29 (12.507) pg/mL at EOT/ET, with a mean (SD) change of -26.47 (42.769) pg/mL (-19.59%).

The iPTH status (Normal, Not clinically significant, or Clinically significant) of all subjects remained unchanged after start of burosumab treatment and throughout the study.

Four subjects reported TEAEs of blood parathyroid hormone increased (3 were considered related to study drug), of whom 1 subject reported a pre-existing condition of blood parathyroid hormone increased at Baseline (see above).

Glomerular Filtration Rate

For the limited eGFR results available, a slight decrease was observed. The result should be interpreted with caution due to the limited sample size. Two subjects were reported with TEAEs of GFR decreased, which were considered not related to study drug. Of note, eGFR was removed from exclusion criterion 3 following Protocol Version 3.0 Amendment 4 since the equation used was not developed and validated in infants below 12 months of age.

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

No clinically meaningful changes from Baseline were observed for vital signs, physical findings or other observations related to safety in Study BUR-CL207.

All the measurements of QT interval, QTcB interval, and QTcF interval were ≤ 450 msec throughout the study. Fourteen subjects experienced a maximum change from Baseline of ≤30 msec for QT interval, QTcB interval, and QTcF interval, and 1 subject experienced a maximum change from Baseline of >30 msec and ≤60 msec for these measurements. No TEAEs were reported for these abnormalities.

Safety in special populations

Intrinsic Factors

As the number of subjects enrolled into Study BUR-CL207 was limited, no meaningful conclusions regarding intrinsic factors can be drawn from the available data. There were no notable differences in the overall incidence of TEAEs across the three cohorts of subjects, which varied by age and starting dose of burosumab.

The safety analyses in Study BUR-CL207 indicated that burosumab treatment was well tolerated in paediatric subjects < 1 year of age, and the safety profile was similar to that observed in previous studies investigating paediatric subjects 1 year of age and older.

Extrinsic Factors

Currently, there are no safety data demonstrating a relationship to any extrinsic factors that may affect the use of burosumab.

Drug Interactions

No drug interaction studies have been conducted with burosumab.

Overdose

No cases of toxicity due to overdose have been reported with burosumab in Study BUR-CL207.

Drug Abuse

There is no known abuse or dependence potential, and given the mechanism of action of this antibody, abuse or dependence is highly unlikely to be an issue.

Withdrawal and Rebound

To date, withdrawal of burosumab results in a decrease of serum phosphate levels to baseline levels. No adverse events have been associated with discontinuation of burosumab therapy or re-treatment.

Discontinuation due to adverse events

No adverse events have been associated with discontinuation of burosumab therapy or re-treatment.

Post marketing experience

Burosumab is currently approved in > 30 countries/regions for the treatment of XLH or both XLH and TIO. The specific indication wording and approved patient age varies by country/region, the minimum approved age being 6 months (including in the US).

Post-marketing case reports describing use of burosumab in patients < 1 year of age

Review of data in the global safety database up to the cut-off date of 30 Sep 2024 revealed a total of 50 case reports (5 serious, 45 non-serious) reporting patients aged < 1 year who received treatment with burosumab. The 50 case reports concerning patients aged < 1 year described 92 events, of which eight were serious. The reported SAEs were Liver function test increased, Surgery, Craniosynostosis, Pericardial effusion, Electroencephalogram, Seizure, Cardiac operation and Hospitalisation. Where reported, event outcomes were resolved (2). None of the SAEs were considered to be related to burosumab by the MAH.

A total of three patients aged < 1 year reported AESIs (all non-serious) in the categories of injection site reactions (n=2; PTs: Injection site reaction and Injection site pain) and hyperphosphataemia (n=1; PT: Blood phosphorus abnormal). As well as the AESIs as defined in the protocol for Study BUR-CL207, events pertaining to infections, craniosynostosis and kidney health were also monitored; review of the global safety database revealed two case reports reporting two events (both non-serious) pertaining to infections and one case report describing one serious event pertaining to craniosynostosis. No events pertaining to kidney health were identified in patients aged < 1 year in the global safety database. The AESIs and additional monitored events are summarised below.

Injection site reaction

Review of data in the global safety database revealed a total of two case reports describing two non-serious events pertaining to injection site reaction in patients aged < 1 year. The reported PTs were Injection site reaction and Injection site pain. No information was provided regarding event outcome; both events were considered related to burosumab by the MAH.

Hyperphosphataemia

Review of data in the global safety database revealed one case report describing one non serious event pertaining to hyperphosphataemia (PT: Blood phosphorous abnormal) in a patient aged < 1 year. The event outcome was not reported, and no information was provided regarding action taken with burosumab. The event was considered related to burosumab by the MAH.

Infections

Review of data in the global safety database revealed a total of two case reports describing two events (both non-serious) pertaining to infection in patients aged < 1 year. The events were COVID-19 and Ear infection; information regarding the outcomes of the events were not reported. Both events were considered unrelated to burosumab by the MAH.

Craniosynostosis

Review of data in the global safety database revealed one case report describing one serious event of Craniosynostosis (Grade 3) in a patient aged < 1 year. Two weeks prior to initiating treatment with burosumab, the patient underwent a head X-ray and computed tomography scan and was diagnosed with craniosynostosis on the same day. Post vault reconstruction surgery to correct sagittal synostosis was scheduled for approximately 1 month later, after which, the event was considered resolved. The subject received one dose of burosumab prior to surgery (but after craniosynostosis diagnosis); treatment with burosumab restarted approximately 2 weeks after the surgery. The event was considered unrelated to burosumab by the MAH due to the patient's age, underlying disease, the fact that craniosynostosis can occur in metabolic bone diseases including XLH, and as craniosynostosis was present prior to the start of treatment with burosumab.

2.5.1. Discussion on clinical safety

The total exposure in subjects <1 year of age in the study was 772 patient weeks. Mean exposure time was 48 weeks.

At least one treatment-emergent adverse event (TEAE) was reported from all subjects. The most commonly reported System Organ Class (SOC) was Infections and infestations (15/16 subjects, 94%). This included five cases of COVID-19. The high incidence of infections in a paediatric population is anticipated. Overall, the pattern of TEAE is compatible with the known safety profile for burosumab and/or is representative for common conditions in the normal paediatric population.

There were no fatal events in Study BUR-CL207. Two subjects experienced a total of two treatment-emergent SAEs: Joint dislocation and craniosynostosis, respectively. The event of Joint dislocation was noted prior to burosumab administration, and therefore a causal association could be excluded. The SAE of Craniosynostosis was considered related to the study drug by the Investigator but unrelated by the MAH. The issue of craniosynostosis being an adverse reaction to burosumab treatment or a manifestation of XLH has been extensively discussed in procedure EMEA/H/C/004275/LEG/008. It was agreed not to label craniosynostosis for burosumab. This issue is however being followed by targeted questionnaires and in the PSURs. This event does not warrant any additional actions.

Adverse events of special interests (AESI) for burosumab are Injection Site Reactions, Hypersensitivity Reactions, Ectopic Mineralisation, Increased Serum Intact Parathyroid Hormone Level, Infections, and Craniosynostosis. No new and unexpected safety issues emerged from the BUR-CL207 study population. Of note, there were no TEAEs of Hyperphosphataemia in the study.

There seem to be no consistent shifts in S-calcium, U-calcium, or PTH during treatment. However, all result should be interpreted with caution due to the very limited sample size.

The MAH puts forward that the theoretical safety concerns for burosumab use in infants relate primarily to the potential for altered calcium-phosphate homeostasis in the context of immature renal and parathyroid functions. However, available evidence indicates that these regulatory systems mature rapidly during the first months of life. Consequently, any transient imbalance in calcium-phosphate homeostasis, such as mild hyperphosphataemia or hypercalcaemia, is expected to be limited to the early post-natal period, when growth-related mineral fluxes are greatest (Smeets, 2022; Sharma, 2016; Taylor-Miller, 2021). In the opinion of the MAH, such risks can be effectively mitigated through conservative dose initiation and close biochemical monitoring.

In addition, the MAH sought input from two leading international experts in paediatric phosphate metabolism and XLH (see Discussion on clinical efficacy). Both confirmed that no additional safety risks are anticipated in infants ≥ 4 months, as renal phosphate handling and parathyroid function are mature and comparable to older children. For infants < 4 months, they advised that the only theoretical concern relates to heightened physiological phosphate reabsorption, which can be effectively managed through conservative initial dosing (0.4 mg/kg Q2W) and close biochemical monitoring.

Crysvita is approved from six months of age in some markets, including the US. The recommended starting dose is 1 mg/kg for patients weighing <10 kg and 0.8 mg/kg for patients weighing >10 kg. The MAH has searched the company global safety data base (GSDB) for case reports pertaining to use in children <12 months of age. In total, 65 case reports were identified; 38 cases occurred in patients aged 6 to < 12 months and 22 cases in patients aged < 6 months. Of the 22 cases in the younger age cohort, 3 cases were reported in children < 1 month of age, 14 cases in children 1-<4 months, and 3 cases in children 4-<6 months. The reason to start treatment (symptoms, hypophosphataemia, or other) in the youngest children is not known. No details on e.g., the number of given doses in each age group, are available. In the majority of the cases (children aged 6 to < 12 months, 58% [22/38 cases], infants aged 1 month to < 6 months, 84% [16/19]), no AEs were reported following the administration of burosumab. In both age groups, no reports of hyperphosphataemia, hypercalcaemia or related complications were identified. It is agreed with the MAH that most reported events were either well-characterised adverse drug reactions or unrelated to treatment. There was also no difference in the frequency of reported AEs between different age groups.

Taken together the benign safety data from the very limited study population in Study BUR-CL207, the indication of renal functional maturity in infants from 1 months supporting extrapolation from older children, and the limited post-marketing experience with no indication of a worse safety profile in children below the age of 12 months, it is agreed that, with a low starting dose and a conservative titration, treatment from 1 months of age is acceptable.

All three vials of Crysvita contain a sorbitol concentration of 45.9 mg/mL. According to the MAH's calculations, the maximum dose of Crysvita, 2.0 mg/kg, administered from a 10 mg/mL vial to subjects 6-12 months of age results in a sorbitol dose of 9.2 mg/kg, i.e. exceeding 5 mg/kg which is the sorbitol threshold for subjects with hereditary fructose intolerance (HFI). In fact, all doses exceeding 1 mg/kg would exceed this threshold in this age group, if the 10 mg/mL vial is used. In the age cohort 1 to <6 months of age, the maximum daily sorbitol dose on the day of administration will not exceed the threshold for subjects with HFI. The required warning against use in subjects with HFI has already been included in section 4.4 for Crysvita. No additional actions with regards to subjects with HFI were considered warranted.

There seem to be limited information regarding potential risk of subcutaneous sorbitol in infants without HFI. No agreed acceptable daily intake (ADI) for SC sorbitol in infants can be identified, but a proposed cutoff for oral intake is 140 mg/kg/d for all age groups (see e.g., Bobillot et al, Potentially Harmful Excipients: State of the Art for Oral Liquid Forms Used in Neonatology and Pediatrics Units - PMC). Of note, there seems to be no other EU-approved medical products for subcutaneous administration with sorbitol as excipient intended for repeated doses in infants. The MAH summarised the very limited data from the literature and from the experience of Crysvita on sorbitol exposure in infants. According to the MAH, no adverse events have been reported postmarketing in infants without HFI. The small theoretical risk of any adverse events due to sorbitol as excipient is not considered to outweigh the benefits of early treatment with Crysvita.

2.5.2. Conclusions on clinical safety

The safety analysis in Study BUR-CL207 did not identify any new or unexpected safety issue. Notwithstanding, the total study population was 16 subjects of which four where under six months of age and none was under four months. Taken together the benign safety data from the very limited study population in Study BUR-CL207, the indication of renal functional maturity in infants from 1 months supporting extrapolation from older children, and the limited post-marketing experience with no indication of a worse safety profile in children below the age of 12 months, it could be agreed that, with a low starting dose and a conservative titration, treatment from 1 months of age is acceptable.

The small theoretical risk of any adverse events due to sorbitol as excipient is not considered to outweigh the benefits of early treatment with 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. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning against the use of Crysvita in children with XTL under 1 month of age has been added to the product information. The Package Leaflet has been updated accordingly.

2.6.1. 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 current package leaflet of Crysvita (burosumab). The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Burosumab (KRN23) is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the excess biological activity of FGF23.

Crysvita is currently approved for the following indications:

- *treatment of X-linked hypophosphataemia, in children and adolescents **aged 1** to 17 years with radiographic evidence of bone disease, and in adults.*
- *treatment of 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.*

The currently sought indication is:

- *treatment of X-linked hypophosphataemia in infants **from 1 month** to 1 year of age **with hypophosphatemia** (see section 5.1), in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults.*
- *treatment of 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.*

Paediatric Posology:

- The approved recommended starting dose for children and adolescents aged 1 to 17 years is 0.8 mg/kg of body weight given subcutaneously every two weeks. Doses should be rounded to the nearest 10 mg. The maximum dose is 90 mg.
- The proposed starting dose in children from 1 month to 6 months of age is 0.4 mg/kg of body weight given every two weeks. Doses should be rounded to the nearest 1 mg. The proposed maximum dose is 0.8 mg/kg.
- The proposed starting dose in children from 6 months to 1 year of age is 0.8 mg/kg of body weight given every two weeks. Doses should be rounded to the nearest 1 mg. The maximum proposed dose is 2 mg/kg.

In the entire paediatric population, the dose may be increased stepwise every fourth week if fasting serum phosphate is below the reference range for age. Recommended increments are 0.2 - 0.4 mg/kg for children 1-<6 months and 0.4 mg/kg for children 6-<12 months.

3.1.1. Disease or condition

X-linked hypophosphataemia (XLH) is a genetic disease caused by loss of function mutations in the PHEX gene. In the absence of a functional PHEX gene, release of FGF23 by osteocytes is greatly increased. High levels of circulating FGF23 causes excessive urinary phosphate excretion and resultant chronic hypophosphataemia, which leads to defective bone mineralisation and progressive musculoskeletal dysfunction if left untreated. Elevated FGF23 levels also suppress 1,25(OH)2D production, resulting in decreased intestinal absorption of calcium and phosphate.

The estimated incidence ranging from 1 in 60,000 to 1 in 20,000 live births.

3.1.2. Available therapies and unmet medical need

Conventional treatment for XLH consists of multiple daily doses of oral phosphate therapy often combined with active vitamin D metabolites (i.e., calcitriol and alfacalcidol). However, conventional treatment is only partially effective and does not specifically target the underlying pathophysiology of skeletal disease in XLH to prevent or improve many of its profound multisystem complications.

There is currently no other product specifically addressing the underlying pathophysiology. Crysvita is currently approved from the age of 12 months in the EU. In other markets, e.g., the US, Crysvita is indicated from the age of six months.

Since manifestations of XLH may occur before 12 months of age, it is agreed that there is an unmet medical need for specific treatments of XLH also in younger children.

3.1.3. Main clinical studies

Study BUR-CL207 was a multicentre, uncontrolled, open-label trial in paediatric patients from birth to < 1 year of age conducted in six European countries. The study comprised a total treatment period of up to 48 weeks. All enrolled subjects received burosumab.

Eligibility criteria included age <12 months at burosumab treatment initiation, a diagnosed PHEX mutation or variant of uncertain significance in either the subject or a directly related family member with appropriate X-linked inheritance, and serum phosphate levels below the age-specific lower limit of normal (LLN) at screening.

In total, the study enrolled 16 subjects.
The study population comprised of three cohorts based on age and starting dose: cohort 1 (6–12 months, starting dose 0.4 mg/kg; n=3), cohort 2 (6–12 months, starting dose 0.8 mg/kg; n=9) and cohort 3 (0-<6 months, starting dose 0.4 mg/kg; n=4).
No subject below the age of 4 months was enrolled in the study.

3.2. Favourable effects

The primary objective of Study BUR-CL207 was safety. Secondary objectives included pharmacodynamic (PD) markers and selected efficacy parameters.

The main PD markers were serum phosphate and serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).

An increase in **serum phosphate** from baseline to end of treatment/early termination (EOT/ET) was seen in all cohorts (Table 10)

Serum $1,25(OH)_2D$ concentrations increased from baseline to EOT/ET after burosumab treatment increased in all cohorts except Cohort 2 (Table 10).

3.3. Uncertainties and limitations about favourable effects

All data are derived from a single, open-label, uncontrolled study. The study population is very limited (n=16). Only four subjects under six months were included, and none of these were under four months of age.

In the approved paediatric population, increases in serum phosphate were seen to translate into a positive effect on Radiographic Global Impression of Change Score (RGI-C), Total Rickets Severity Score (RSS) and growth velocity. Rickets becomes apparent only with the onset of weight bearing. Subjects' RGI-C scores and RSSs were documented throughout the study in order to evaluate these

endpoints; however, these scores have never been evaluated in paediatrics < 1 year of age, and a clinically meaningful interpretation of "change from Baseline" in this young patient population may be impaired when signs of rickets have not yet developed by study entry. The large inter-individual variation in growth in combination with the very limited study population hampers meaningful interpretation of the mean height-for-age z-scores in the study population, which decreased during treatment.

Serum phosphate samples for evaluation of effect and for dose adjustments are normally collected after at least a 4-h-fasting period. This may not be possible with infants. Limited data from Study BUR-CL207 however indicate that fasting deviation had little effect on serum phosphorus levels.

From an efficacy point of view, with a long-term treatment goal and dose titration based on serum phosphate, it is not considered crucial to have a high starting dose.
The approved starting dose in the paediatric population ≥12 months is 0.8 mg/kg with possibility to dose titrate with increments of 0.4 mg/kg every 4 weeks up to a maximum dose of 2 mg/kg or 90 mg, based on fasting serum phosphate two weeks after dose. This posology was used in Study BUR-CL207. However, for safety reasons, the first cohort and the youngest cohort in Study BUR-CL207 used a starting dose of 0.4 mg/kg.
A starting dose of 0.4 mg/kg and a maximum dose of 0.8 mg/kg is proposed in subjects from 1 month to 6 months. In addition, smaller dose increment per escalation step, i.e. 0.2 – 0.4 mg/kg is proposed This is agreed.
In the US, Crysvita is indicated for treatment of XLH from 6 months of age. The recommended starting dose is 1 mg/kg for patients weighing <10 kg and 0.8 mg/kg for patients weighing ≥10 kg. The MAH has summarised data from the literature, from an American registry study and from Study BUR-CL207. The reported starting doses begin at 0.8 mg/kg with a maximum dose of 2 mg/kg. The experience in children 6-<12 months is overall very limited, but there are no reports of hyperphosphataemia in the summary. To further mitigate the risk of hyperphosphataemia, the MAH has accepted to extend the monitoring of fasting serum phosphate after treatment initiation and dose adjustment. This further ensures an appropriate treatment. Hence, the proposed starting dose, dose increment, and frequency of up-titration in paediatric patients aged ≥6 to <12 months are considered acceptable.

3.4. Unfavourable effects

The total exposure in subjects <1 year of age in the study was 772 patient weeks. Mean exposure time was 48 weeks.

At least one treatment-emergent adverse event (TEAE) was reported from all subjects. The most commonly reported System Organ Class (SOC) was Infections and infestations (15/16 subjects, 94%). This included five cases of COVID-19.

There were no fatal events in Study BUR-CL207.

Two subjects experienced a total of two treatment-emergent SAEs: Joint dislocation and craniosynostosis, respectively. The event of Joint dislocation was noted prior to burosumab administration, and therefore a causal association could be excluded.

Adverse events of special interests (AESI) for burosumab are Injection Site Reactions, Hypersensitivity Reactions, Ectopic Mineralisation, Increased Serum Intact Parathyroid Hormone Level, Infections, and Craniosynostosis. In total, nine AESI were reported. Four events of increased PTH were reported. No other preferred term was reported by more than one subjects. One event each of nephrocalcinosis and craniosynostosis were reported.

3.5. Uncertainties and limitations about unfavourable effects

The study enrolled only 16 subjects. Only four children were < 6 months of age, all of which 4-6 months.

The issue of craniosynostosis being an adverse reaction to burosumab treatment or a manifestation of XLH has been extensively discussed in procedure EMEA/H/C/004275/LEG/008. No amendments to the SmPC were however deemed necessary. An additional SAE of craniosynostosis was reported in the study.

From a safety perspective, it is considered of importance to avoid overshooting and high peak serum phosphate levels. The population PK model is not considered adequate to simulate the exposure following other doses (or with other covariate combinations) than those administered during the study. As discussed in section 13.3, to mitigate the risk of hyperphosphataemia, further adjustments of the proposed posology are requested.

The product contains sorbitol, which may be harmful to infants in higher concentrations. The acceptable daily intake for sorbitol via subcutaneous injections in infants without hereditary fructose intolerance (HFI) is not firmly established; however, in some publications a maximum intake of 140 mg/mg per os is considered acceptable for all ages. There is a remaining uncertainty about the potential risks with sorbitol as an excipient in medicinal products in infants even in the absence of HFI. Of note, there seems to be no other EU-approved medical products for subcutaneous administration with sorbitol as excipient intended for repeated doses in infants. The MAH has summarised the very limited data from the literature and from the experience of Crysvita on sorbitol exposure in infants. According to the MAH, no adverse events have been reported postmarketing in infants without HFI. The small theoretical risk of any adverse events due to sorbitol as excipient is not considered to outweigh the benefits of early treatment with Crysvita.

3.6. Effects Table

Table 15: ***Effects Table for Crysvita in the treatment of XLH***

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
Serum phosphate	Change from baseline (CFB) Mean (SD)	mg/dL	<u>Cohort 1:</u> BL 2.88 (0.40) EOT/ET 3.54 (0.96) **CFB 0.55 (0.56)** <u>Cohort 2:</u> BL 3.03 (0.38) EOT/ET 3.73 (0.38) **CFB 0.65 (0.38)**	Unc: Open label, uncontrolled study, limited sample size (N=16)	BUR-CL207

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
			Cohort 3: BL 3.36 (0.34) EOT/ET 3.80 (0.21) **CFB 0.44 (0.28)** Total population: BL 3.10 (0.38) EOT/ET 3.71 (0.47) **CFB 0.57 (0.38)**		
Serum $1,25(OH)_2D$	Change from baseline to EOT/ET Mean (SD)	pg/mL	Cohort 1: BL 66.6 (20.7) EOT/ET 70.3 (10.2) **CFB 3.7 (27.3)** Cohort 2: BL 71.4 (46.1) EOT/ET 70.0 (17.6) **CFB -2.50 (55.0)** Cohort 3: BL 50.2 (25.9) EOT/ET 81.4 (20.7) **CFB 31.1 (44.2)** Total population: BL 65.2 (37.5) EOT/ET 73.3 (16.9)	Unc: Open label, uncontrolled study, limited sample size (N=16)	BUR-CL207

Effect	Short description	Unit	Treatment	Uncertainties / Strength of evidence	References
			CFB 8.4 (46.8)		
TEAE	Percentage subjects reporting at least one event	n (%)	16 (100)		BUR-CL207
SAE	Percentage subjects reporting at least one event	n (%)	Cohort 1: 1 (33) Cohort 2: 1 (11) Cohort 3: -		BUR-CL207
AESI	Percentage subjects reporting at least one event	n (%)	Cohort 1: 3 (100) Cohort 2: 5 (56) Cohort 3: 1 (25)	All PTs reported by single subjects except increased PTH (n=4)	BUR-CL207

Abbreviations: $1,25(OH)_2D$: 1,25-dihydroxyvitamin D, BL: baseline; CFB Change from baseline, EOT/ET: end of treatment/early termination, PT: preferred term, PTH: parathyroid hormone, SAE: serious adverse event, TEAE: Treatment - emergent adverse event, Unc: Uncertainties, XLH: X-linked hypophosphataemia
Notes:Cohort 1: Aged ≥ 6 to < 12 months, 0.4 mg/kg starting dose (n=3); Cohort 2: Aged ≥ 6 to < 12 months, 0.8 mg/kg starting dose (n=9); Cohort 3: Aged < 6 months, 0.4 mg/kg starting dose (n=4).
Central laboratory limits of normal for Serum Phosphate: 3.7 to 6.5 mg/dL (1.20 to 2.10 mmol/L) in females and 3.6 to 6.7 mg/dL (1.15 to 2.15 mmol/L) in males.
Central laboratory limits of normal for Serum $1,25(OH)_2D$: 19.9 to 79.3 pg/mL BUR-CL207

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The study population was limited, and all data is derived from a single, open label uncontrolled study. In particular, only four subjects under six months were included, and none of these were under four months of age. As the data from the study did not single-handedly support extension of the indication to subjects < 12 months of age with XLH, an extension of the indication to subjects below one year of age thus required extrapolation of efficacy and safety from the approved XLH populations, i.e. from 1 year and up.

XLH is caused by mutations to the PHEX gene, in turn leading to excessive amounts of circulating FGF23. The genetic mechanism is inborn, independent of age. Burosumab is a monoclonal antibody that binds to and inhibits the excess biological activity of FGF23. This is also anticipated to be

independent of age. This is supported by the observation in the trial that serum phosphate increased to normal levels with burosumab treatment in all three cohorts.

In the approved paediatric population, the increase in serum phosphate was shown to translate into a positive effect on rickets as assessed by e.g., RGI-C and RSS. This observation could be extrapolated also to younger children. In the initial marketing authorisation procedure for the initial paediatric population (EMEA/H/C/4275/0000), only children with radiological evidence of bone disease had been included in the clinical studies. It was then concluded that efficacy could not be extrapolated to subjects without radiological evidence of bone disease. This is reflected in the approved indication. However, it is also recognised that such evidence might not be present in young children, in particular below the age of 6 months, since rickets mainly develops with the onset of weight bearing. Therefore, based on the common pathophysiological mechanism for XLH and mechanism of action of burosumab over all ages, it is possible that a beneficial effect of burosumab could theoretically be extrapolated from the approved populations to younger children.

The MAH presented data from clinical and preclinical studies indicating that phosphate-regulating mechanisms are functionally mature and highly active in early infancy. To further substantiate the physiological basis for extrapolating efficacy and safety in infants, the MAH sought input from two leading international experts in paediatric phosphate/calcium metabolism and XLH. The experts emphasised that renal phosphate handling in infants is intact and highly avid, consistent with the literature cited above, and that no evidence exists of functional renal immaturity that would reduce burosumab efficacy. One expert highlighted that fractional tubular reabsorption of phosphate is higher in infants than in older children, while the other noted that elevated 1,25-dihydroxyvitamin D levels in infancy reflect normal growth demands rather than immaturity of renal hydroxylation. In addition, both confirmed that no additional safety risks are anticipated in infants ≥ 4 months, as renal phosphate handling and parathyroid function are mature and comparable to older children. For infants < 4 months, they advised that the only theoretical concern relates to heightened physiological phosphate reabsorption, which can be effectively managed through conservative initial dosing (0.4 mg/kg Q2W) and close biochemical monitoring.

To further assess safety with burosumab treatment in subjects < 6 months of age. The MAH searched the company global safety data base (GSDB) for case report pertaining to use in children <12 months of age. In total, 65 case reports were identified; 38 cases occurred in patients aged 6 to < 12 months and 22 cases in patients aged < 6 months, of which 15 cases from subjects < 4 months. Among those subjects, most reported adverse events were either well-characterised adverse drug reactions or unrelated to treatment. There was also no difference in the frequency of reported AEs between different age groups.

The MAH's argumentation supporting extrapolation of the effect and safety from children >12 months of age to subjects aged from 1 month to 1 year was considered acceptable. Based on a longer terminal elimination half-life and greater accumulation in paediatric patients aged <12 months compared to paediatric patients aged ≥12 months further adjustments of the proposed posology are requested to mitigate the risk of hyperphosphataemia. In addition, the monitoring of serum phosphate was enhanced.

The required warning for use in subjects with hereditary fructose intolerance (HFI) based on the sorbitol contents was already included in the SmPC. Upon request the MAH discussed the safe use of Crysvita pertaining to subcutaneous sorbitol in subjects <12 months of age without HFI. No safety concerns relating specifically to sorbitol intolerance or sorbitol-related toxicity have been identified in association with burosumab. This is acknowledged. the small theoretical risk of any adverse events due to sorbitol as excipient is not considered to outweigh the benefits in this age cohort.

The potential risks for development or worsening of craniosynostosis and/or nephrocalcinosis were previously discussed in several procedures. Since both conditions are also reported as related to XLH, this hampers the assessment of whether burosumab treatment may also be causally associated to such events. In Study BUR-CL207, one new event each of craniosynostosis and nephrocalcinosis were reported. Assessment of the provided information is not considered to warrant any additional action.

3.7.2. Balance of benefits and risks

In the EU, Crysvita is approved for treatment of X-linked hypophosphataemia, in children and adolescents from 1 to 17 years with radiographic or other evidence of bone disease, and in adults. In some other markets including the US, children from 6 months of age are indicated for treatment. The MAH initially sought an extension of indication to include paediatric patients from birth to 1 year of age. Following the first CHMP assessment and the List of Questions, the applicant revised the proposed indication to patients from 1 month to 1 year of age, in line with the available clinical evidence.

The observed safety profile of burosumab in Study BUR-CL207 was benign. The safety analysis did not identify any new or unexpected safety issues. An expected increase in serum phosphate was seen in all three cohorts in response to burosumab treatment. This is considered to indicate a beneficial effect. Efficacy data beyond pharmacodynamic markers remain limited. The sample size is also limited, as is any post-marketing experience in children <12 months of age. Notwithstanding, the MAH presented support from the literature and from statements by two clinical experts for that the renal phosphate handling in infants is intact from early age. The MAH's argumentation supporting extrapolation of the effect from children >12 months of age to subjects aged from 1 month to 1 year was considered acceptable. Taken together, the benign safety data from the very limited study population in Study BUR-CL207, the indication of renal functional maturity in infants from 1 months supporting extrapolation from older children, and the limited post-marketing experience with no indication of a worse safety profile in children below the age of 12 months, it was concluded that, with a low starting dose and a conservative titration, treatment from 1 month of age is acceptable. The small theoretical risk of any adverse events due to sorbitol as excipient is not considered to outweigh the benefits of early treatment with Crysvita.

3.8. Conclusions

The overall Benefit/Risk of Crysvita is 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 Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of X-linked hypophosphataemia (XLH) in paediatric patients from 1 month to 1 year of age for CRYSVITA, based on final results from study BUR-

CL207; this is a phase 1/2 Open-label, Multicenter, Non-randomized Study to Evaluate Safety, Pharmacodynamics, Pharmacokinetics and Effect of Burosumab in Pediatric Patients from Birth to Less than 1 Year of Age with XLH; As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

The variation leads to amendments to the annex(es) I, and IIIB.

Amendments to the marketing authorisation

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0411/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000263400.

Attachments

1. SmPC (changes highlighted) as adopted by the CHMP on 23 April 2026.