EMA/566422/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

CRYSVITA

International non-proprietary name: burosumab

Procedure No. EMEA/H/C/004275/0000

Note

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

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1. Introduction

On April 29, 2019, the MAH submitted a completed paediatric study for Crysvita, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study is listed as a requirement of the Paediatric Investigational Plan (PIP).
This is also an application for a Post Approval Measure (PAM) to address the specific obligation number 1 (SOB 1) as outlined in Annex II.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Crysvita was granted conditional approval on 19 February 2018 for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.
The current study is part of the clinical development program as it is one of the three special obligations for a potential full approval in the paediatric population, as listed below.

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
1. UX023-CL201 In order to confirm the efficacy and safety of Crysvita in the treatment of X-linked Hypophosphataemia (XLH) in children between 5 and 12 years old, the MAH should submit the updated results of study UX023-CL201, a randomized, open-label, dose finding, phase 2 study to assess the pharmacodynamics and safety of the anti-FGF23 antibody, KRN23, in paediatric patients with XLH.	July 2019
2. UX023-CL301 In order to confirm the efficacy and safety of Crysvita in the treatment of X-linked Hypophosphataemia (XLH) in children between 1 and 12 years old, the MAH should conduct and submit the results of study UX023-CL301, a randomized, open-label, phase 3 Study to assess efficacy, safety and pharmacodynamics of the anti-FGF23 antibody, KRN23, versus oral phosphate and active vitamin D in paediatric patients with XLH.	July 2019
3. UX023-CL205 In order to confirm the efficacy and safety of Crysvita in the treatment of X-linked Hypophosphataemia (XLH) in children between 1 and 4 years old, the MAH should submit the updated results of study UX023-CL205, an open-label, phase 2 study to assess the safety, pharmacodynamics, and efficacy of KRN23 in paediatric patients with XLH.	May 2020

Crysvita is currently not approved for treatment in adult subjects.

2.2. Information on the pharmaceutical formulation used in the study

Most (45/52, 87%) were receiving commercially available product. Two were receiving burosumab under a temporary authorization, 2 were receiving burosumab under the Sponsor's Ultra Care Bridge, and 3 were receiving burosumab per an early access scheme.

2.3. Clinical aspects

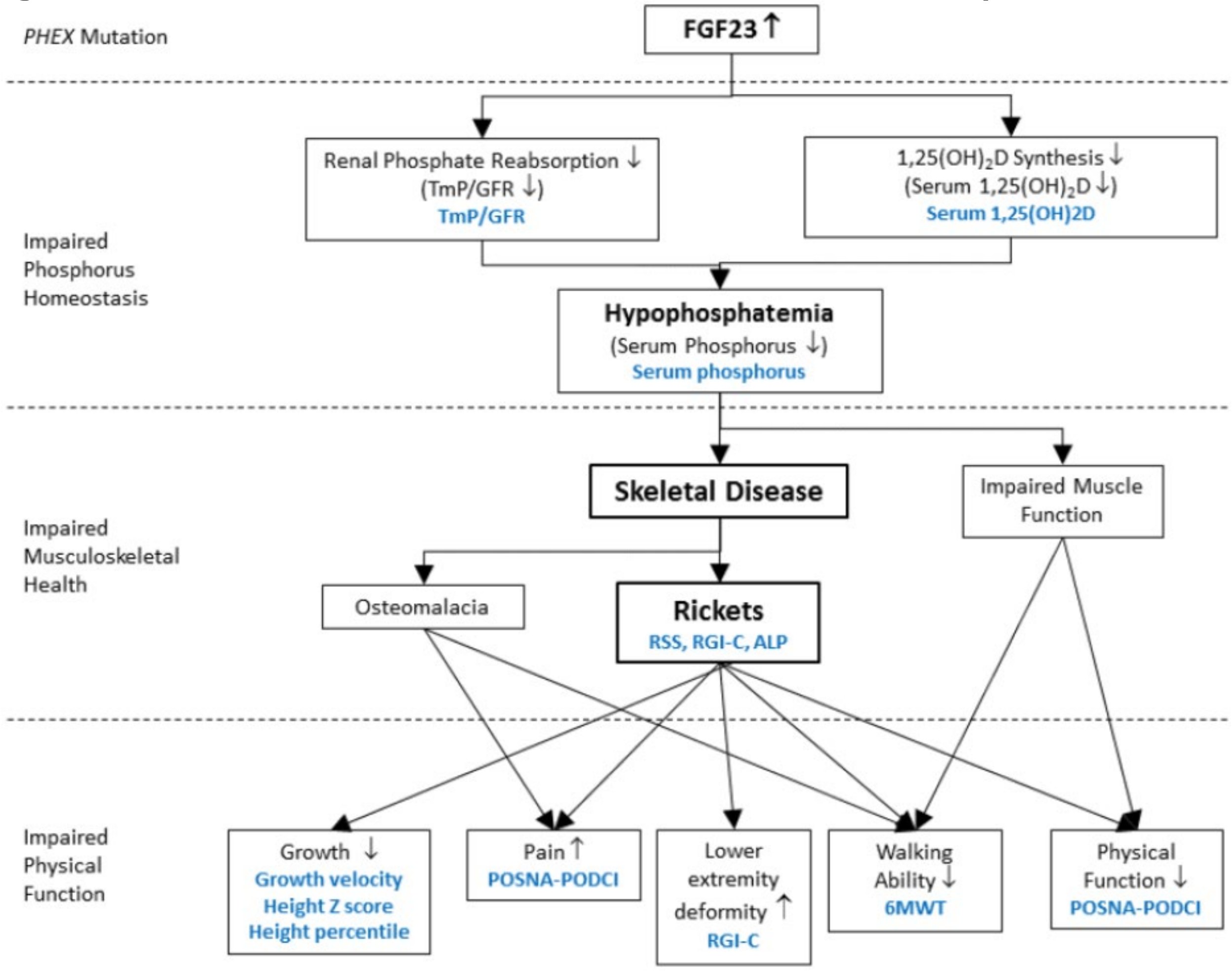
2.3.1. Introduction

The MAH submitted a final report for:

- **Study UX023-CL201**: A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)

X-linked hypophosphatemia (XLH) is a hereditary disease characterized by high levels of circulating fibroblast growth factor 23 (FGF23) that lead to excessive urinary phosphate excretion and subsequent hypophosphataemia (Figure 1).

Figure 1: XLH Pediatric Disease Characteristics and Associated Endpoints



ALP = alkaline phosphatase; 1,25(OH)2D = 1,25-dihydroxyvitamin D; 6MWT = 6-Minute Walk Test; POSNA-PODCI = Pediatric Orthopedic Society of North America - Pediatric Outcomes Data Collection Instrument; RGI-C = Radiographic Global Impression of Change; RSS = Rickets Severity Score; TmP/GFR = ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate; XLH = X-linked hypophosphatemia

Crysvita is a fully human monoclonal antibody designed to bind and thereby inhibit the excessive biologic activity of FGF23.
The European Commission granted a conditional marketing authorization (CMA) for Crysvita on 19 February 2018 for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons. The EU launch date was April 2018.

The benefits and risks of burosumab in children with XLH were demonstrated in the original MAA based on the single-arm studies UX023-CL201 and UX023-CL205. Data up to Week 64 for all subjects in Study UX023-CL201 were available at the time for the CMA. For a full approval, the MAH should complete the following studies as specific obligations:

- UX023-CL201
- UX023-CL205
- UX023-CL301

In an ongoing variation (EMEA/H/C/4275/II/04), Week 64 data from the confirmatory phase 3 Study UX023-CL301, is currently under assessment.

2.3.2. Clinical study

Study UX023-CL201: *A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Paediatric Patients with X-linked Hypophosphatemia (XLH)*

Description

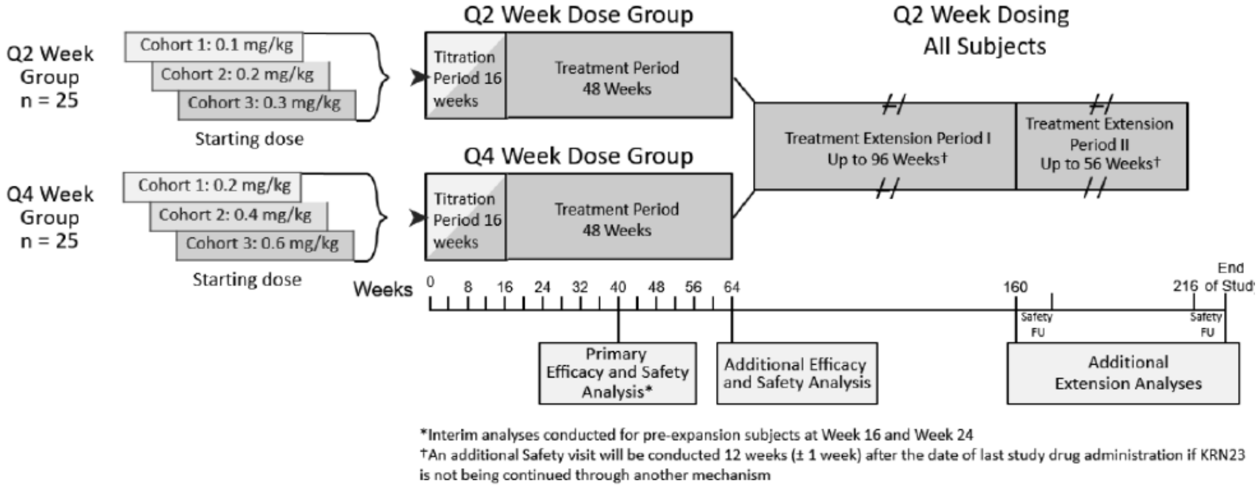
Methods

Assessor's comment
The methodology for Study UX023-201 was thoroughly assessed in procedure EMEA/H/C/4275 at the original marketing approval for Crysvita and is therefore only briefly summarised below.

Study design

UX023-CL201 was a randomized, multicentre, open-label, dose-finding Phase 2 study assessed the PD, efficacy, and safety of burosumab in prepubescent children (5 to 12 years old) with X-linked Hypophosphatemia (XLH) (Figure 1).

Figure 2: Schema for Study UX023-CL201



Q2 = every 2 weeks; Q4 = monthly

The goal of the Treatment Extension Period I (Weeks 64 to 160) was to evaluate the long-term safety and efficacy of burosumab. During the Treatment Extension Period I, all subjects received burosumab Q2W. Analyses of long-term safety and efficacy was conducted during and at the completion of Treatment Extension Period I.

Subjects could choose to end participation in the study at Week 160 and complete an EOS efficacy visit (referred to as EOS I). For subjects who chose to continue after Week 160, the study also included a Treatment Extension Period II (up to 56 weeks). The aim of the Treatment Extension Period II (Weeks 160 to 216) was to continue to provide burosumab treatment to study subjects until the availability of a separate rollover study (or other mechanism of treatment) or through September 2018, while also continuing to collect long-term safety and efficacy data. The duration of Treatment Extension Period II varied for individual subjects and was determined by the time from Week 160 through the EOS II Visit.

During the Treatment Extension Period II, all subjects received burosumab Q2W.

Study population /Sample size

Approximately 30 subjects with XLH and radiographic evidence of bone disease ("pre-expansion subjects") were planned for enrolment. The study was expanded to include additional subjects ("expansion subjects") who were required to have rickets severity of at least 1.5 at the knee (per the Rickets Severity Score [RSS] method), for a total of approximately 50 subjects planned overall.

The main eligibility criteria were age 5-12, diagnosis of XLH, low serum phosphorus and radiographic evidence of active bone disease (or, for expansion subjects, an RSS score in the knee of at least 1.5).

Treatments

All subjects received burosumab Q2W or Q4W at doses given in Figure 1. Dosing was then adjusted individually according to a pre-established protocol. From Week 64, all subjects were treated Q2W.

Outcomes/endpoints

The primary efficacy analysis was change from Baseline in severity of rickets as measured by RSS total score assessment of wrist and knee radiographs. The primary analysis for efficacy and safety endpoints was Week 40.

Key PD endpoints were serum phosphorus, serum 1,25(OH)2D, and ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR) (TmP/GFR).

Statistical Methods

Statistical tests were 2-sided at the alpha=0.05 significance level, and 2-sided 95% confidence intervals (CIs) were used. All p-values were presented as nominal p-values. No adjustment on multiplicity was made. For the primary efficacy endpoint of change in RSS total score, the difference between the 2 dose regimens (Q2W and Q4W) was summarized with 95% CIs.

For repeated measures, the generalized estimating equation (GEE) approach was used for assessing the change over time. The GEE model included regimen, study visit and interaction between regimen and study visit as categorical variables.

Results

Assessor's comment

This AR focusses on data from the not previously assessed Treatment Extension Period I and II, i.e. week 64-160 and week 160 to End of study. Data up to week 64 was thoroughly assessed in procedure EMEA/H/C/4275 at the original marketing approval for Crysvita and are therefore not repeated here. Subject disposition and baseline data are briefly summarised.

Recruitment/ Number analysed

A total of 52 paediatric subjects were enrolled into the study and were randomized 1:1 to the Q2W (26 subjects) and Q4W (26 subjects) regimens. All 52 subjects completed 160 weeks on study, and no subject discontinued from the study.

Per subjects' Safety Follow-up visits or telephone calls, all 52 subjects were receiving burosumab after their last dose on Study UX023-CL201.

Baseline data

Sex: 28 (54%) females; 24 (46%) males

Age: mean (SD): 8.5 (1.87) years; range: 5 to 12 years

Race: 89% White, 4% Black or African-American, 8% Other

Dosing

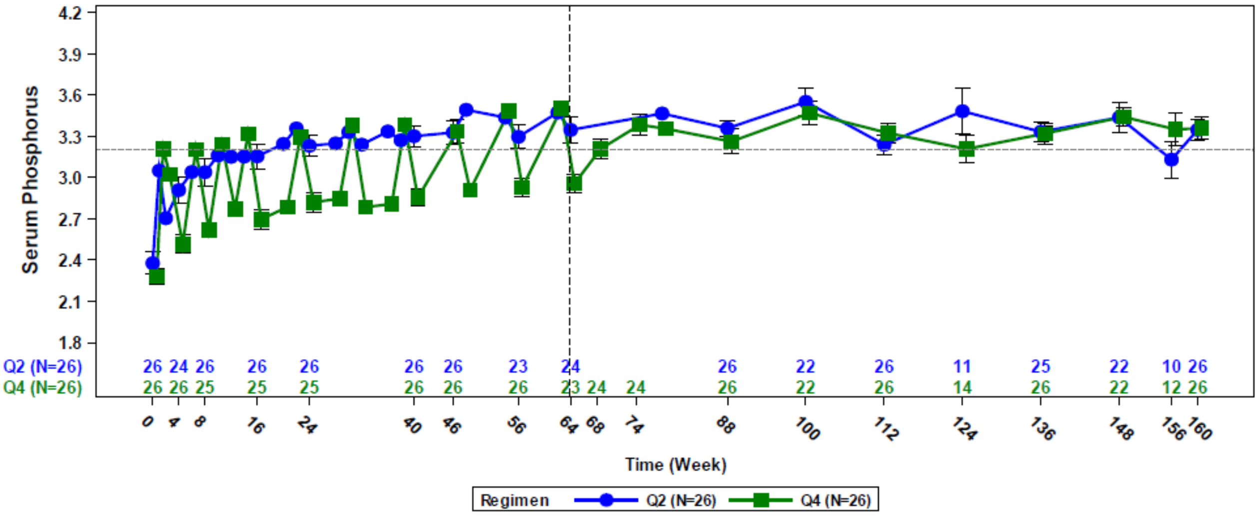
Mean burosumab dose per administration at Week 64 for the Q2W group was 1.05 mg/kg and for the Q4W group 1.01 mg/kg. At Week 160, the mean dose was 1.05 mg/kg and at Week 190 1.07 mg/kg. By Week 214, data were available for only 3 subjects.

Assessor's comment
The mean burosumab dose per administration was unchanged from Week 64 to Week 190.

PD RESULTS

Serum phosphorus level

Figure 3: Serum Phosphorus Level (mg/dL) (Mean ± SE) by Regimen (PK/PD Analysis Set)

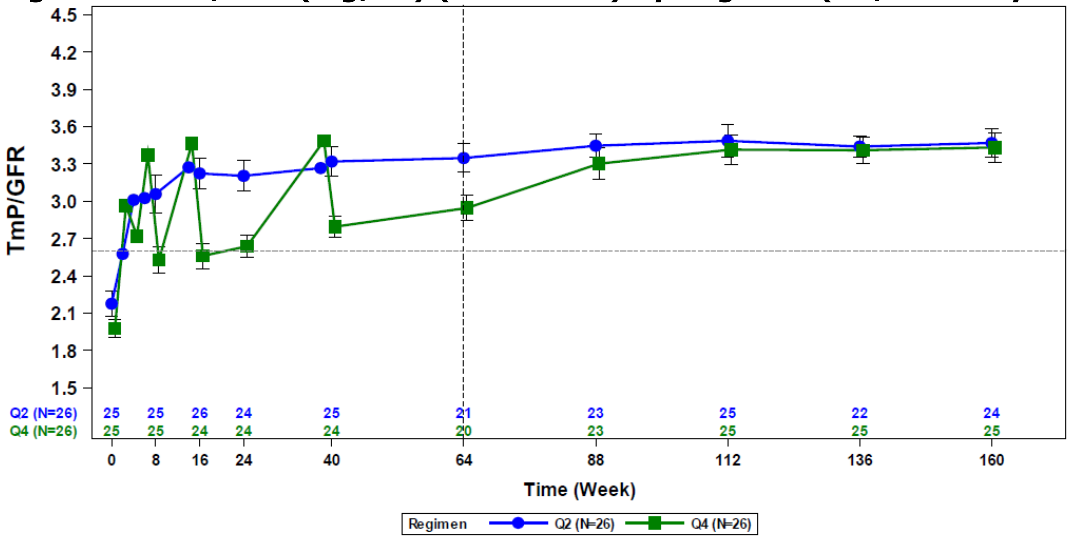


Note: Starting at Week 64, all subjects received burosumab Q2W.
Note: Horizontal dashed line indicates the lower limit of the reference range, 3.2 mg/dL. Vertical dashed line at Week 64 indicates transition from Q4W→Q2W dosing. SE bars are displayed only at selected visits.

Phosphate Reabsorption

Renal phosphate reabsorption is impaired in patients with XLH due to excess FGF23. TmP/GFR is a measure of renal phosphate reabsorption, the primary mechanism by which FGF23 regulates phosphate homeostasis by comparing the fractional absorption of phosphate relative to the estimated rate of glomerular filtration, which provides insight into the degree to which phosphate is being reabsorbed relative to the amount of glomerular filtrate.

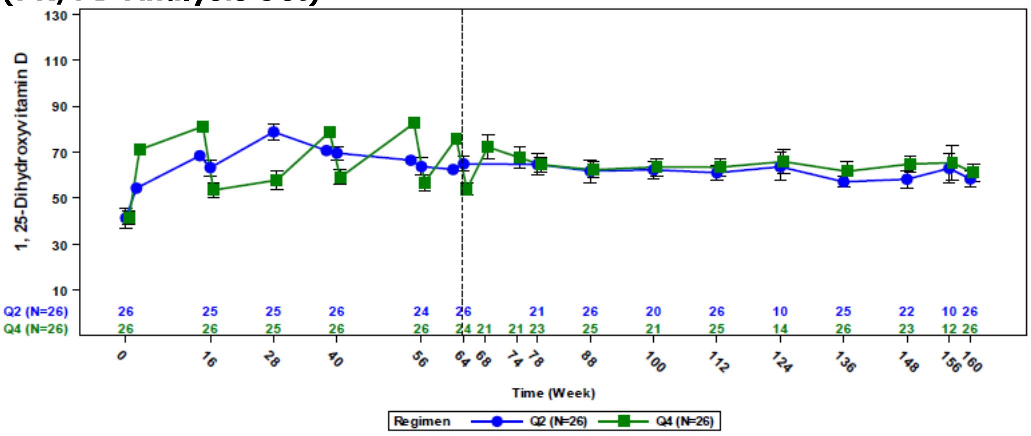
Figure 4: TmP/GFR (mg/dL) (Mean ± SE) by Regimen (PK/PD Analysis Set)



Note: Starting at Week 64, all subjects received burosumab Q2W.
Note: Horizontal dashed line indicates the lower limit of the reference range, 3.2 mg/dL (1.03 mmol/L). Vertical dashed line at Week 64 indicates transition from Q4W→Q2W dosing. SE bars are displayed only at selected visits.

Serum 1,25(OH)2D

Figure 5: Serum 1,25-Dihydroxyvitamin D Level (pg/mL) (Mean ± SE) by Regimen (PK/PD Analysis Set)



Assessor's comment
The effect of burosumab given Q2W on the pharmacodynamic parameters serum phosphate levels, phosphate reabsorption and Serum 1,25(OH)2D were maintained from Week 64 to Week 160.

Biomarkers of Bone Turnover

Table 1: Change from baseline in bone turnover markers (PK/PD Analysis Set) (Compiled from CSR by the Assessor)

	P1NP Mean change from baseline (%)	CTx Mean change from baseline (%)
Week 40	+37	+43
Week 64	+20	+50
Week 88	+27	+59
Week 112	+25	+47

Assessor's comment
P1NP, a marker of bone formation, and CTx, a marker of bone resorption, increased during the study. The increase in bone turnover markers was maintained from Week 64.

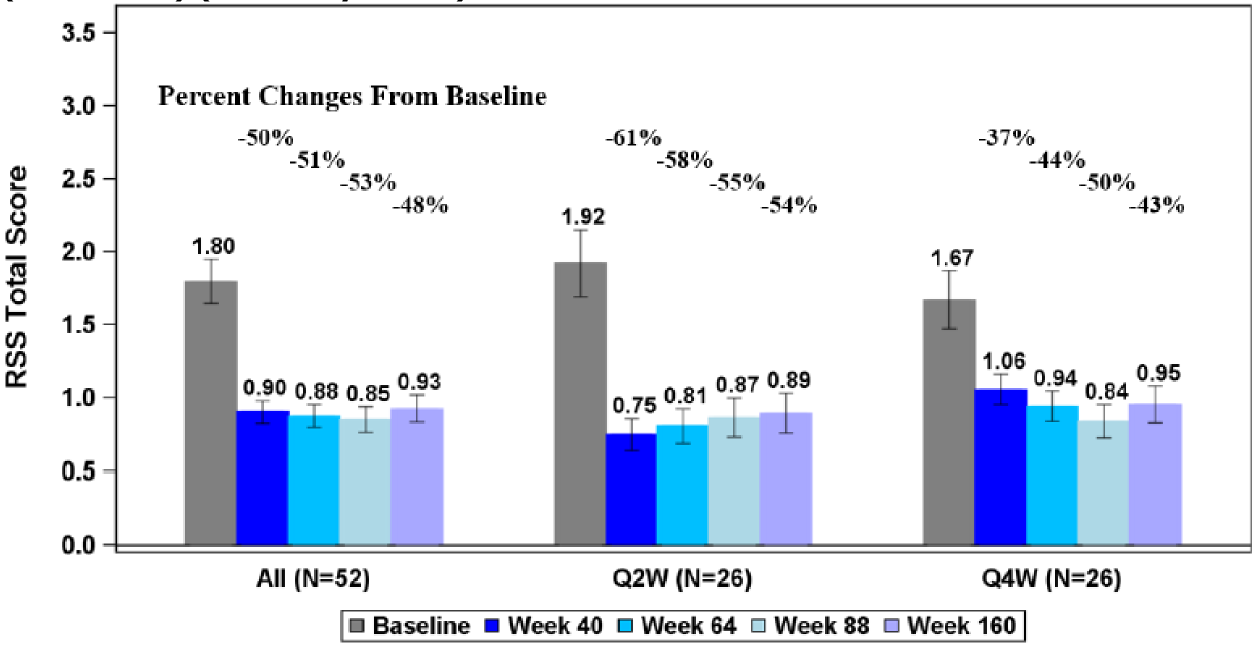
EFFICACY RESULTS

RSS Total Score Change from Baseline (Primary Efficacy Endpoint)

The Thacher Rickets Severity Score (RSS) is a radiographic scoring system that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, lucency, and cupping, as well as the proportion of growth plate affected. A single, central, independent rater performed all RSS ratings for all radiographs for this study. For the RSS assessment, disease improvement is expressed as a negative number, i.e., decreased severity of rickets. The usual range of observed scores for subjects with XLH is between 0 and 6.5, depending on severity and prior treatment.

RSS total score are presented in Figure 6. At Week 160, 10 subjects had fused or partially fused growth plates, and 1 subject did not have a wrist X-ray; therefore, RSS total score was available for 41 subjects.
At the EOS, 1 additional subject had fused growth plates.

Figure 6: RSS Total Scores at Baseline, Week 40, Week 64, Week 88, and Week 160 (Mean ± SE) (ITT Analysis Set)



GEE = generalized estimation equation; ITT = intent to treat; Q2W = every 2 weeks; Q4W = monthly; RSS = Rickets Severity Score
Change from Baseline to Weeks 40, 64, 88, and 160, per GEE model: $p < 0.0001$ for All, Q2W, and Q4W
Note: Week 88: Q4W group, N = 25; Overall, N = 51. Week 160: Q2W group, N = 19; Q4W group, N = 22; Overall, N = 41
Note: Starting at Week 64, all subjects received burosumab Q2W.

Assessor's comment

Efficacy as determined by RSS was maintained to Week 160, even though the percent change from baseline in the Q2W group was lower at Week 88 and Week 160 compared to Week 40 (-55%, -54% and -61%, respectively). Seven subjects in the Q2W arm were excluded from the Week 160 analysis due to fused or partially fused growth plates.

RSS Responder Analysis

RSS data were analysed using the prespecified responder definition, i.e. subjects with a Baseline RSS total score ≥ 1.0 (m) who had a reduction in RSS total score from Baseline of at least 1.0 at the indicated time point (n)

Table 2: RSS Responders at Week 40, 64, 88, and 160 by Dose Regimen (ITT Analysis Set)

	Burosumab Regimen		
	Q2W (N = 26)	Q4W→Q2W (N = 26)	Overall (N = 52)
RSS Responders (n/m [%])			
Week 40	16/20 (80.0%)	12/19 (63.2%)	28/39 (71.8%)
Week 64	16/20 (80.0%)	12/19 (63.2%)	28/39 (71.8%)
Week 88	14/20 (70.0%)	13/18 (72.2)	27/38 (71.1)
Week 160	8/14 (57.1%)	9/15 (60.0%)	17/29 (58.6)

Assessor's comment

After Week 64, the RSS responder rate gradually decreases in the Q2W population. A similar development is not seen in the Q4W arm, presumably due to the dose increase to Q2W at Week 64.

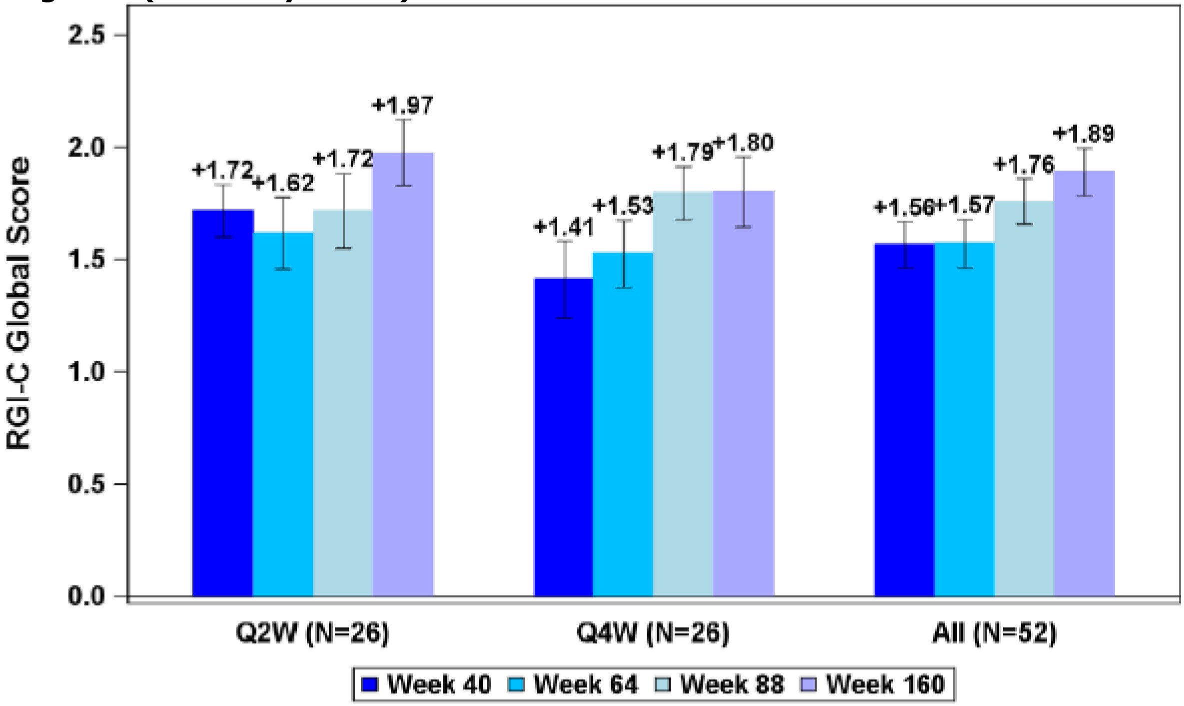
In the Q2W arm, responder rate was 80% (16/20) at Week 64, 70% (14/20) at Week 88 and 57% (8/14) at Week 160. The difference in population between Week 64 and Week 160 is explained by a number of subjects being excluded from the Week 160 analysis due to fused or partially fused growth plates.

RGI-C Scores

The RGI-C (Radiographic Global Impression of Change) utilizes a 7-point ordinal scale to evaluate the extent of healing in a radiograph as compared with a radiograph taken at a prior time point. Ratings of -3, -2, and -1 between the 2 time points assessed indicate severe, moderate, and minimal worsening, respectively, and ratings of +1, +2 and +3, indicate minimal healing, substantial healing, or complete/near complete healing, respectively. Unlike the RSS system, for which radiographs are individually scored independent of any other radiographs, clinical significance is explicit in RGI-C due to the comparison with a previous radiograph. Three paediatric radiologists not affiliated with the conduct of the study and contracted by a central imaging facility independently evaluated and provided RGI-C scores for pairs of wrist, knee, and long leg radiographs. The average of the scores assigned by the 3 independent raters were used for analysis. For the RGI-C assessment, in contrast with RSS assessment, disease improvement is expressed as a positive number, i.e., increased healing of rickets.

Only 41 subjects were evaluable for analysis of RSS at Week 160; 10 subjects had fused growth plates, and 1 subject did not have a wrist X-ray. A sensitivity analysis conducted on the 41 subjects with open growth plates at Week 160 showed RGI-C scores over time that were consistent with the overall study population.

Figure 7: RGI-C Global Scores at Weeks 40, 64, 88, and 160 (Mean ± SE) by Dose Regimen (ITT Analysis Set)

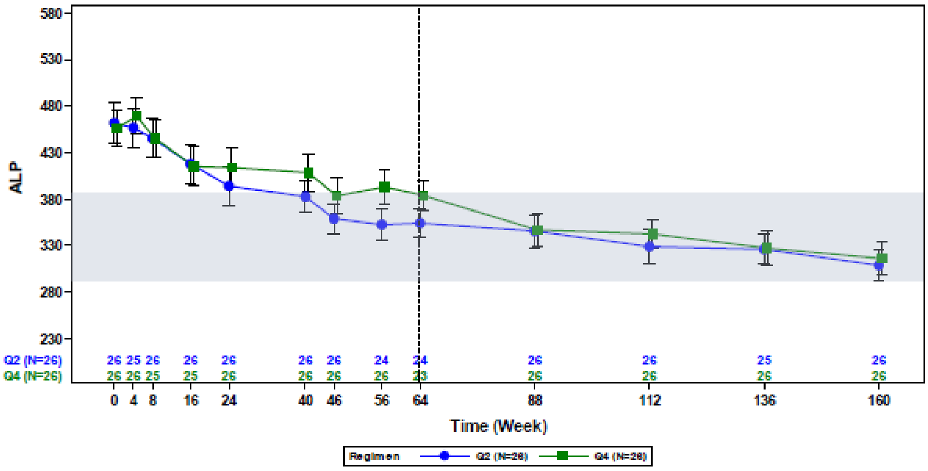


Assessor's comment
The validity of the RGI-C scoring was thoroughly discussed in procedure EMEA/H/C/4275 at the original marketing approval for Crysvita. Efficacy as determined by RGI-C was maintained to Week 160.

Serum markers of rickets – ALP and BALP

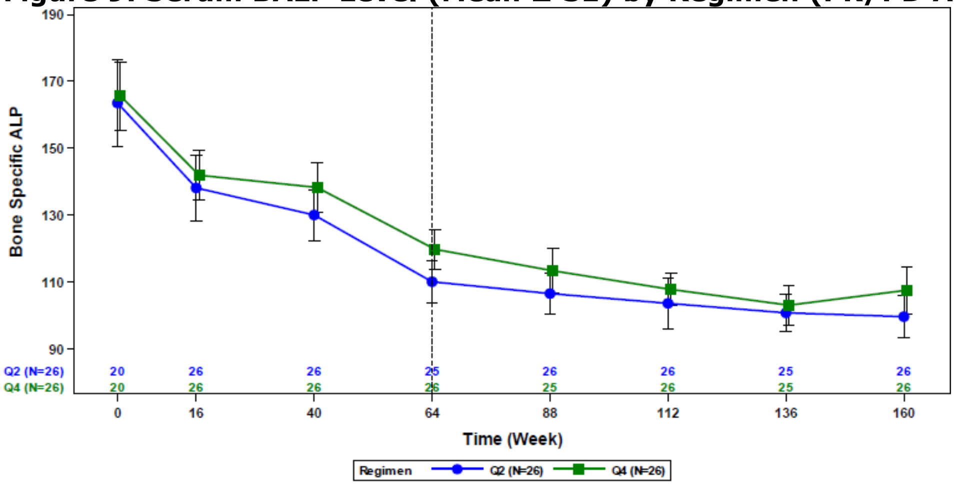
Total and bone-specific alkaline phosphatases (ALP and BALP) are elevated in the presence of rickets, and the magnitude of elevation correlates with the magnitude of rickets.

Figure 8: Serum ALP Level (U/L) (Mean ± SE) by Regimen (PK/PD Analysis Set)



Grey bar indicates the ULN ranges, approximately 297 to 385 U/L, depending on the age and sex of the child.
Vertical dashed line at Week 64 indicates transition from Q4W to Q2W

Figure 9: Serum BALP Level (Mean ± SE) by Regimen (PK/PD Analysis Set)



Vertical dashed line at Week 64 indicates transition from Q4W to Q2W

Assessor's comment

Decrease in ALP and BALP continued from Week 64 to Week 160.

At Week 160, the mean ALP level was 312 (88) U/L. The reference range for ALP varies with age and gender with upper and lower limit of normal for the study population at approximately 297-362 U/L and 42-96 U/L, respectively.

Changes in standing height

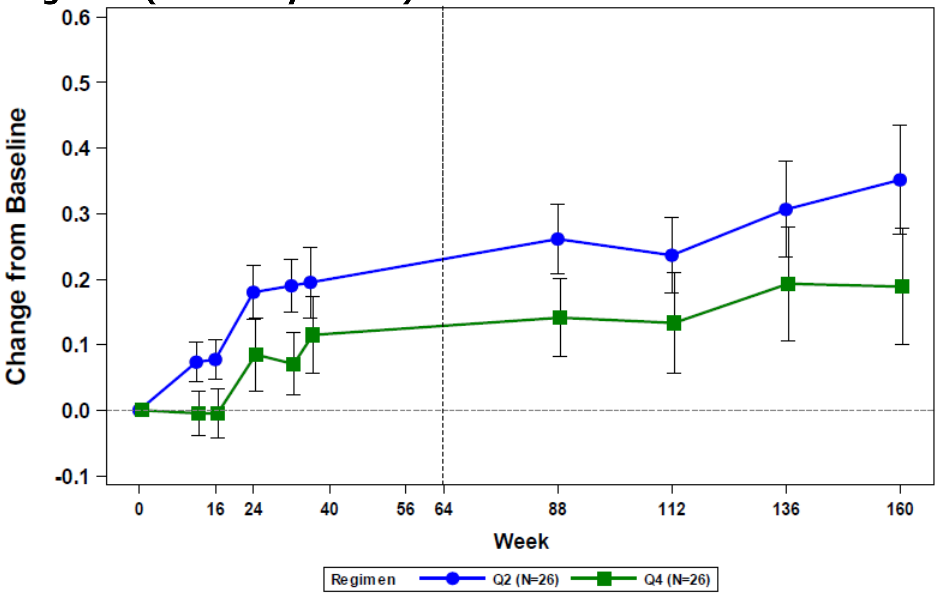
Change in standing height was assessed as velocity (assessed using a model-based approach based on all standing height data obtained during the study) (Table 3), Z score, and percentile for age and gender.

Table 3: Growth Velocity (cm/year) at Baseline, Week 0 to Week 64, Week 64 to Week 112, and Week 112 to Week 160 Based on Standing Height by Dose Regimen (ITT Analysis Set)

	Burosumab Regimen		
Growth Velocity[a]	Q2W (N = 26)	Q4W→Q2W (N = 26)	Overall (N = 52)
Baseline			
n	25	24	49[b]
cm/year, mean (SD)	5.45 (1.171)	5.24 (1.402)	5.35 (1.280)
Week 0 to Week 64			
n	25	24	49[b]
cm/year, mean (SD)	6.14 (1.466)	5.67 (1.215)	5.91 (1.354)
Change from Baseline, mean (SD)	+0.73 (1.399)	+0.37 (2.164)	+0.55 (1.804)
p-value[c]	0.0160	0.4114	0.0376
Week 64 to Week 112			
n	25	24	49[b]
cm/year, mean (SD)	5.74 (1.728)	5.33 (2.662)	5.54 (2.220)
Change from Baseline, mean (SD)	+0.29 (2.284)	+0.09 (2.523)	+0.19 (2.381)
p-value[c]	0.5335	0.8606	0.5750
Week 112 to Week 160			
n	25	24	49[b]
cm/year, mean (SD)	6.12 (1.914)	5.78 (2.452)	5.95 (2.177)
Change from Baseline, mean (SD)	+0.67 (2.318)	+0.54 (3.158)	+0.61 (2.733)
p-value[c]	0.1627	0.4096	0.1273

a Data presented for subjects with evaluable growth velocity data at Baseline. Baseline growth velocity was calculated based on the standing height measured within 2 years prior to Baseline.
b Growth velocity could not be calculated for 3 subjects for whom pre-treatment height data were not available within 2 years prior to Baseline.
c The One sample t test was used for p-value and 95% CI on growth velocity (cm/year) change from Baseline

Figure 10: Standing Height Z Score Change from Baseline (LS Mean ± SE) by Dose Regimen (ITT Analysis Set)



LS mean and SE were calculated from a GEE model, which included visit, regimen, visit by regimen, and gender as factors, and age and standing height Z-score at baseline as covariates, with exchangeable covariance structure.
Vertical dashed line at Week 64 indicates transition from Q4W to Q2W

Assessor's comment

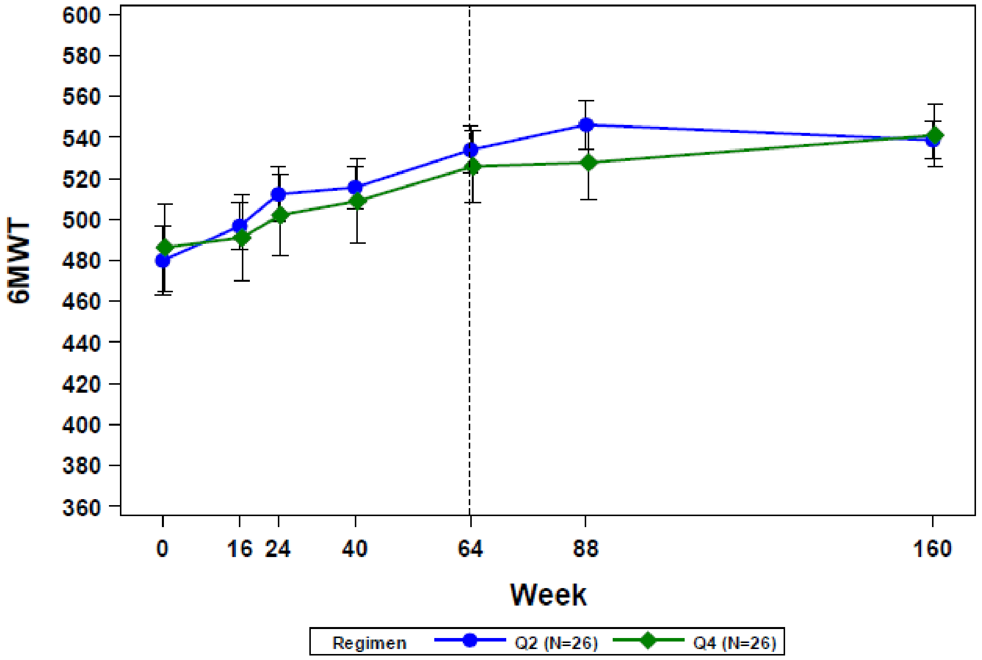
In the Q2W arm, mean growth velocity was comparable during Week 0-64 and Week 112-160 (6.14 cm/year and 6.12 cm/year, respectively versus 5.45 cm/year at baseline). During Week 64-112, on the other hand, mean growth velocity was lower (5.74 cm/year). It is difficult to find a reasonable explanation for this phenomenon.

Of note, subjects in the Q4W treatment arm do not seem to catch up with the subjects in the Q2W arm in standing height even after transition to the Q2W dosing at Week 64. This supports the chosen posology Q2W.

Walking Ability by 6MWT

The 6-minute walking test (6MWT) distance provides an indicator of mobility and physical functioning

Figure 11: 6MWT Distance Walked (m) (Mean ± SE) to Week 160 by Regimen (ITT Analysis Set)

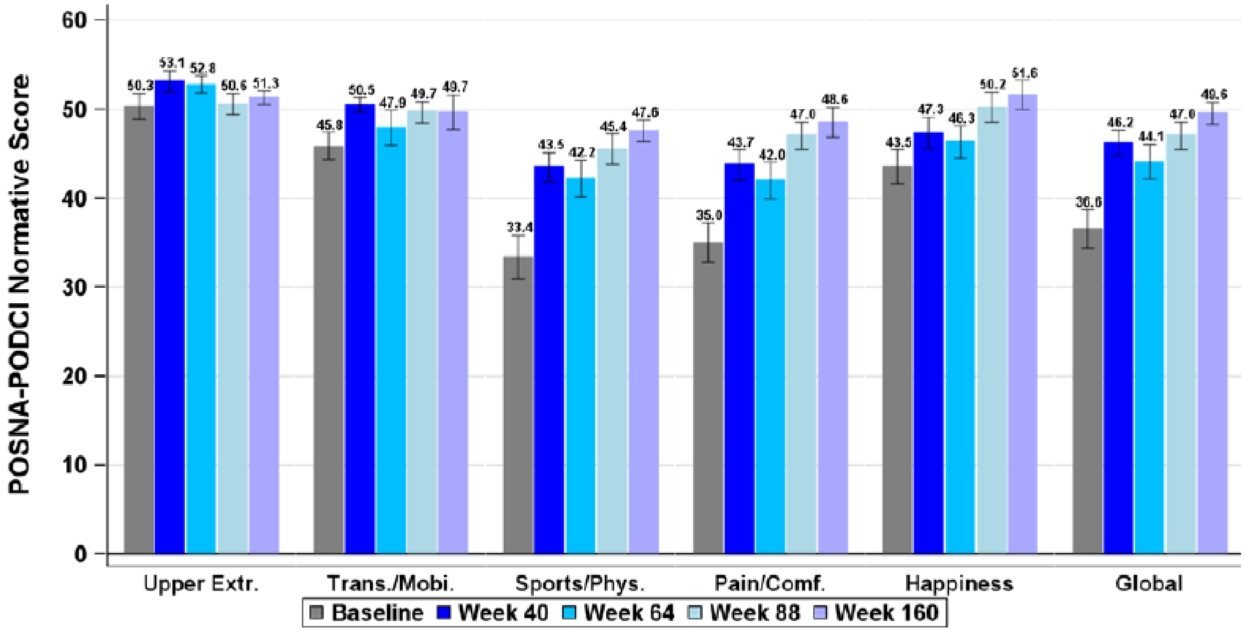


Assessor's comment
No further increase in 6MWT distance was seen between Week 88 (+65 m compared to baseline) and Week 160 (+57 m) in the Q2W treatment arm. This is notable. As the mean age increased by 72 weeks, i.e. almost 1.5 years, between Week 88 and Week 160, a longer 6MWT distance at Week 160 would have been expected.

Functional Disability and Pain

The POSNA-PODCI (Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument) questionnaire was used to measure the impact of bone and muscle conditions on daily activities and health-related quality of life. The following scales were administered in this study: Upper Extremity and Physical Function, Transfers and Basic Mobility, Sports/ Physical Functioning, Pain/Comfort, and Happiness. Scores from the first four scales, excluding the Happiness domain, are combined to derive a Global Functioning Scale score. Raw scores are scaled to set the mean of the normal population at 50 and one standard deviation in the normal population equal to 10. A score of 40 is therefore considered at the lower boundary of the normal range for this instrument, and scores in the 30s and 20s imply a significant level of physical impairment and pain.

Figure 12: POSNA-PODCI Scales (Mean [SE] Normative Scores) at Baseline and Weeks 40, 64, 88, and 160 (ITT Analysis Set)



Assessor's comment
The self-assessment of Functional Disability and Pain according to the POSNA-PODCI scales showed sustained improvement on the Sports/ Physical Functioning, Pain/Comfort, Happiness and global scales up to Week 160.

SAFETY RESULTS

All Adverse Events

Table 4: Summary of Treatment-emergent Adverse Events (Safety Analysis Set)

	Q2W (N = 26) n (%)	Q4W→Q2W (N = 26) n (%)	Overall (N = 52) n (%)
All TEAEs	26 (100.0%)	26 (100.0%)	52 (100.0%)
Serious TEAE	0 (0.0%)	1 (3.8%)	1 (1.9%)
Related TEAE	17 (65.4%)	21 (80.8%)	38 (73.1)
Serious Related TEAE	0 (0.0%)	1 (3.8%)	1 (1.9%)
Grade 3 or 4 TEAE	1 (3.8%)	1 (3.8%)	2 (3.8%)
TEAE Leading to Study Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAE Leading to Treatment Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAE Leading to Death	0 (0.0%)	0 (0.0%)	0 (0.0%)

The most frequent TEAEs (> 40% incidence) were headache (75%), cough (69%), vomiting (56%), arthralgia (54%), nasopharyngitis (54%), pain in extremity (52%), ISR (50%), oropharyngeal pain (50%), pyrexia (48%), upper respiratory tract infection (48%), injection site erythema (44%), and rhinorrhoea (42%)

Table 5: Related, Treatment-emergent Adverse Events – Preferred Terms by Descending Order in the Overall Study Population (Safety Analysis Set)

Preferred Term	Q2W (N = 26) n (%)	Q4W→Q2W (N = 26) n (%)	Overall (N = 52) n (%)
Subjects with any related, treatment-emergent adverse events	17 (65.4)	21 (80.8)	38 (73.1)
Injection site reaction	11 (42.3)	13 (50.0)	24 (46.2)
Injection site erythema	10 (38.5)	9 (34.6)	19 (36.5)
Injection site bruising	2 (7.7)	4 (15.4)	6 (11.5)
Injection site pruritus	2 (7.7)	4 (15.4)	6 (11.5)
Injection site swelling	5 (19.2)	1 (3.8)	6 (11.5)
Injection site pain	3 (11.5)	2 (7.7)	5 (9.6)
Pain in extremity	3 (11.5)	2 (7.7)	5 (9.6)
Vitamin D deficiency	1 (3.8)	4 (15.4)	5 (9.6)
Arthralgia	2 (7.7)	2 (7.7)	4 (7.7)
Injection site rash	2 (7.7)	2 (7.7)	4 (7.7)
Abdominal pain upper	2 (7.7)	1 (3.8)	3 (5.8)
Myalgia	1 (3.8)	2 (7.7)	3 (5.8)
Blood 1,25-dihydroxycholecalciferol increased	0 (0.0)	2 (7.7)	2 (3.8)
Blood parathyroid hormone increased	1 (3.8)	1 (3.8)	2 (3.8)
Diarrhoea	2 (7.7)	0 (0.0)	2 (3.8)
Erythema	1 (3.8)	1 (3.8)	2 (3.8)
Headache	1 (3.8)	1 (3.8)	2 (3.8)
Injection site induration	1 (3.8)	1 (3.8)	2 (3.8)
Nausea	2 (7.7)	0 (0.0)	2 (3.8)
Peripheral swelling	1 (3.8)	1 (3.8)	2 (3.8)
Pruritus	1 (3.8)	1 (3.8)	2 (3.8)
Rash	2 (7.7)	0 (0.0)	2 (3.8)
Urticaria	1 (3.8)	1 (3.8)	2 (3.8)
Vomiting	1 (3.8)	1 (3.8)	2 (3.8)
Abdominal discomfort	1 (3.8)	0 (0.0)	1 (1.9)
Abdominal pain	0 (0.0)	1 (3.8)	1 (1.9)
Application site erythema	0 (0.0)	1 (3.8)	1 (1.9)
Back pain	1 (3.8)	0 (0.0)	1 (1.9)
Blood 25-hydroxycholecalciferol decreased	1 (3.8)	0 (0.0)	1 (1.9)
Bone pain	1 (3.8)	0 (0.0)	1 (1.9)
Contusion	1 (3.8)	0 (0.0)	1 (1.9)
Dizziness	0 (0.0)	1 (3.8)	1 (1.9)
Dry skin	1 (3.8)	0 (0.0)	1 (1.9)
Ear pain	0 (0.0)	1 (3.8)	1 (1.9)
Epistaxis	1 (3.8)	0 (0.0)	1 (1.9)
Eye pain	1 (3.8)	0 (0.0)	1 (1.9)
Hypercalcaemia	0 (0.0)	1 (3.8)	1 (1.9)
Injection site discolouration	1 (3.8)	0 (0.0)	1 (1.9)
Injection site discomfort	0 (0.0)	1 (3.8)	1 (1.9)
Injection site haematoma	0 (0.0)	1 (3.8)	1 (1.9)
Injection site haemorrhage	0 (0.0)	1 (3.8)	1 (1.9)
Injection site pallor	1 (3.8)	0 (0.0)	1 (1.9)
Injection site urticaria	0 (0.0)	1 (3.8)	1 (1.9)
Lip swelling	0 (0.0)	1 (3.8)	1 (1.9)
Musculoskeletal pain	0 (0.0)	1 (3.8)	1 (1.9)
Nephrocalcinosis	1 (3.8)	0 (0.0)	1 (1.9)
Non-cardiac chest pain	0 (0.0)	1 (3.8)	1 (1.9)
Pain	1 (3.8)	0 (0.0)	1 (1.9)
Pallor	0 (0.0)	1 (3.8)	1 (1.9)
Pyrexia	0 (0.0)	1 (3.8)	1 (1.9)
Rash pustular	0 (0.0)	1 (3.8)	1 (1.9)
Tooth abscess	1 (3.8)	0 (0.0)	1 (1.9)
Vitamin D decreased	0 (0.0)	1 (3.8)	1 (1.9)

Assessor's comment

At the end of study, 73% of the subjects had experienced at least one related TEAE, compared to 69% at the time of the conditional marketing approval (CMA). No TEAE leading to death or discontinuation has been reported. The spectrum of adverse events is generally in line with previously reported adverse events with Crysvita.
Of note, the frequency of headache events observed in this study (75%) is higher than published reviews of epidemiological studies on headache in children and adolescents, which have found a prevalence of headache in this population of approximately 54% to 58%.

Among the related TEAEs, no new events of abnormalities in vitamin D or Calcium homeostasis were reported after the CMA of Crysvita.

Serious Adverse Events

One subject in the study UX023-CL201 experienced two concurrent serious TEAEs (pyrexia and myalgia) starting at Day 336, i.e. at approximately 48 weeks. Eosinophil percentage was 14.2% while other white cell differential parameters were in the normal range, which later normalized. The subject was negative for anti-KRN23 antibodies at all time points. No action was taken with KRN23 in response to the events, and study treatment was ongoing as of the data cut-off for this report, with no interruptions in the subsequent study dosing regimen. The SAEs were assessed as moderate in severity and deemed possibly related to KRN23.

Assessor's comment

No new serious adverse event was reported after the CMA of Crysvita.

Adverse Events of special interest

Injection Site Reactions

Table 6: Summary of Injection Site Reaction TEAEs During the Study (Safety Analysis Set)

	Q2W (N = 26) n (%)	Q4W→Q2W (N = 26) n (%)	Overall (N = 52) n (%)
Subjects with any treatment-emergent injection site reaction adverse events (per MedDRA high-level term "Injection site reactions")			
During the study	19 (73.1)	18 (69.2)	37 (71.2)
Weeks 0-64	17 (65.4)	13 (50.0)	30 (57.7)
Weeks 64-112	12 (46.2)	12 (46.2)	24 (46.2)
Weeks 112-160	7 (26.9)	9 (34.6)	16 (30.8)

Assessor's comment

The reporting rate of injection site reaction was comparable, or somewhat lower, during Weeks 112-160 to that during the first 112 weeks of the study.

Hypersensitivity

Assessor's comment
After the conditional marketing approval (CMA) of Crysvita, an additional five subjects (in total 28 subjects; 54%) have reported hypersensitivity adverse events at the end of study. None of the events were considered related to treatment.

Hyperphosphataemia

Assessor's comment
No TEAEs with the PT hyperphosphataemia were reported during the study, and no subject experienced serum phosphorus levels above the normal range at any time during the study. It should be noted that no postprandial phosphate samples were analysed.

Ectopic Mineralization

One subject experienced an adverse event of ectopic mineralization (moderate nephrocalcinosis), considered possibly related to study drug by the investigator, that was noted at the Week 40 Visit.

The Week 88 and Week 112 renal ultrasound assessments demonstrated the absence of nephrocalcinosis. The event had resolved by the Week 136 Visit. Per the reporting investigator, the renal ultrasound report at Week 40 suggested a "beginning of nephrocalcinosis"; however, nephrocalcinosis scores per the central reading were 0 at Screening and at Weeks 16, 40, 64, 88, 112, 136, 160, and EOS. Nephrolithiasis was observed at Week 112 but not at any other renal ultrasound assessment during the study

The presence of nephrocalcinosis was evaluated based on a 5-point scale ranging from 0 (normal) to 4 (stone formation).

Table 7: Shifts in Nephrocalcinosis Scores at Week 160 by Renal Ultrasound (Safety Analysis Set)

Baseline Score[a]	Baseline (N = 52) n (%)	Week 160 Score (m = 52) n (%)			
		0	1	2	3
0	34 (65.4%)	30 (57.7%)	3 (5.8%)	1 (1.9%)	-
1	11 (21.2%)	3 (5.8%)	4 (7.7%)	4 (7.7%)	-
2	7 (13.5%)	-	-	5 (9.6%)	2 (3.8%)

Note: m = number of subjects with assessments at both Baseline and at Week 160. Percentages are based on the total number of subjects (N = 52). Shaded cells indicate no change from Baseline.
a Nephrocalcinosis was scored based on a 5-point scale

One subject had a renal ultrasound nephrocalcinosis score of zero at Screening, a score of 1 from Week 16-112, and a score of 2 at Week 136-160. eGFR, iPTH, and serum calcium were normal, and 24-hour urine calcium excretion rate was not increased, except at Week 160 (5 mg/kg/day [normal is < 4 mg/kg/day]).

Assessor's comment

The reported event of ectopic mineralisation was discussed in procedure EMEA/H/C/4275. As all central readings of ultrasound assessments were negative for nephrocalcinosis from baseline up to Week 88 in this subject, "beginning of nephrocalcinosis" at the clinical site's renal ultrasound report at Week 40 was considered less probable. This is further supported by the report that the central readings were 0 also at Weeks 112, 136, 160, and EOS.

Nine subjects had increases of 1 point in renal ultrasound scores during the study and 3 subjects had decreases of 1 point. One subject had an increase in renal ultrasound score of 2 points from 0 to 2. No reports of increases in renal ultrasound scores >1 point was presented at CMA. Ectopic mineralisation is listed as an important potential risk in the Crysvita RMP and labelled in section 4.4 of the Crysvita SmPC. This is considered adequate.

Restless Legs Syndrome

No TEAEs of restless legs syndrome were reported during the study

Gastrointestinal Adverse Events

Gastrointestinal adverse events were considered related to study drug by the investigator for 6 subjects (12%).

Dental Adverse Events

Children with XLH may present with severe dental defects which typically manifest as spontaneous infections leading to dental abscesses. These infections are a result of defective dentin and enamel hypoplasia that diminishes the layer surrounding the pulp chamber, enabling oral bacteria to enter the pulp chamber and form abscesses.

For the periods Week 0-64, Week 64-112, and Week 112-160, the overall exposure-adjusted incidence of dental TEAEs was 0.10, 0.09, and 0.03 events/year, respectively.
The exposure-adjusted incidences in those periods were 0.06, 0.06, and 0.02 events/year, respectively, for toothache and 0.03, 0.03, and 0.01 events/year, respectively, for tooth abscess.

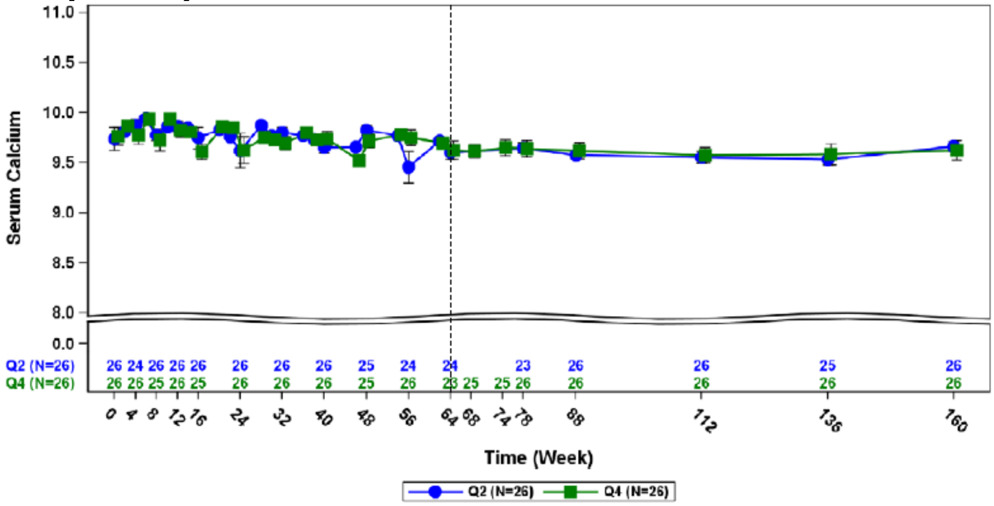
Assessor's comment

The exposure-adjusted incidence for dental TEAEs including tooth abscesses were numerically somewhat lower during Week 112-160.

Clinical Laboratory Evaluations

Serum Calcium

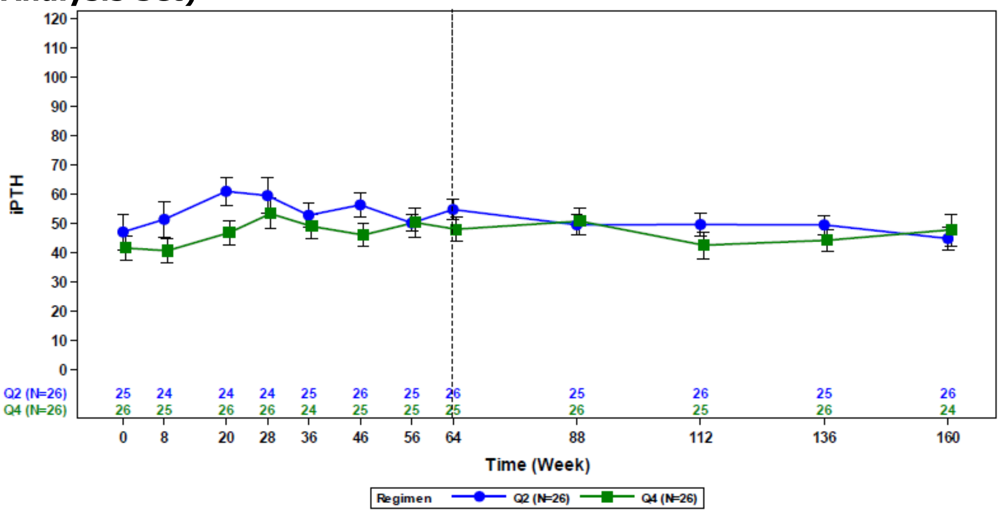
Figure 13: Serum Calcium Concentration (mg/dL) (Mean ± SE) by Regimen (Safety Analysis Set)



Assessor's comment
No clinically meaningful changes from baseline were noted in mean serum calcium during the course of the study. No events of hyper- or hypocalcaemia was reported in the study after the CMA.

Serum iPTH

Figure 14: Serum iPTH Concentration (pg/mL) (Mean ± SE) by Regimen (Safety Analysis Set)



Two subjects had serum iPTH concentrations >2xULN at Screening or Baseline visits. Both subjects showed decreases in serum iPTH concentration over time. Four subjects had transitory postbaseline iPTH concentrations > 2XULN during the study.

Assessor's comment

No clinically meaningful changes from baseline were noted in mean serum iPTH during the course of the study.

One additional event of iPTH > 2XULN was reported in the study after the CMA. This event was reported at Week 208 and had improved at the EOS visit at Week 216.

Vital signs

One subject had a TEAE of mild irregular heart rate on Study Day 924 that was considered definitely not related to study drug and that resolved in 1 day.

Assessor's comment

One additional TEAE, not considered related to the study drug, in the area of vital signs was reported in the study after the CMA

ECG

No subject had QTc intervals (with either Fridericia's [QTcF] or Bazette's [QTcB] corrections) of > 450 ms. Nine subjects had QTc interval increases > 30 ms from Baseline (by either QTcF or QTcB or both). ECG assessments were normal at baseline and abnormal at Weeks 16, 40, 64, 88, 112, and 160 for 2 (4%), 7 (14%), 3 (6%), 6 (12%), 2 (4%), and 1 (2%) subjects, respectively. Clinically insignificant sinus bradycardia was the most common abnormality noted.

Assessor's comment

One additional subject (nine subjects in total) with QTc interval increases > 30 ms bit >60 ms from Baseline was reported in the study after the CMA. No subject had QTc intervals of > 450 ms.

ECHO

Ectopic mineralization (EM), as evaluated by ECHO, is a previously described qualitative echocardiographic index (Gaibazzi et al. 2015) of the possible extent of abnormal cardiac structural calcium or fibrotic deposition in tissue based on increased myocardial ultrasonic intensity (ie, brightness), which was graded from 0 (none) to 8 (marked). EM was Grade 0 for all 52 subjects at Baseline. EM was Grade 0 for all postbaseline assessments except for EM Grade 1 for 2 subjects at Week 88. Both subjects had EM Grade 0 at Weeks 112, 136, and 160 and at the EOS Visit.

Overall cardiac function was assessed by left ventricular ejection fraction (LVEF). The mean (SD) LVEF was within normal limits at Baseline (60% [6.1%]) and remained within normal limits at Week 16 (62% [5.6%]), Week 40 (61% [5.7%]), Week 64 (62% [5.3%]), Week 88 (60% [5.2%]), Week 112 (60% [5.1%]), and Week 160 (60% [4.3%])

Assessor's comment

Two subjects had signs of ectopic myocardial mineralisation grade 1/8 at Week 88. As all other ECHO assessments, both earlier and later, showed no ectopic myocardial mineralisation for both subjects, this is not considered of clinical relevance.

Anti-Burosumab Antibodies

At Baseline, serum samples from 6 subjects (12%) tested positive for anti-burosumab antibodies; 2 [8%] in the Q2W group and 4 [15%] in the Q4W→Q2W group. Two of these subjects (one in each treatment group) tested positive at every visit.

Overall, 6 subjects (12%) who were negative at Baseline were positive at any post-baseline visit, and 2 subjects (4%) who were positive at Baseline were negative at any post-baseline visit.

Three subjects (6%) were positive for neutralizing anti-burosumab antibodies.

The baseline reactivities most likely reflect the presence of pre-existing cross-reactive antibodies. Weak reactivities due to cross-reactive antibodies are sometimes detected, particularly with high sensitivity assays that use a low starting dilution such as 1:2. Furthermore, the assay cut point was set conservatively such that there should be approximately 5% false positive results.

Because only one of the 6 subjects with reactivity with burosumab at Baseline showed a minimal increase in reactivity after exposure to the product, it is unlikely that these represent true anti-drug antibodies.

Assessor's comment

Pre-existing cross-reactive antibodies were present in six subjects at baseline. Three subjects developed neutralising anti-burosumab antibodies during the study. For one subject, presence of neutralising anti-burosumab antibodies was detected more consistently after Week 88 (Weeks 88, 136, 160 and EOS). This subject received 1.5 mg/kg burosumab from Week 54 to EOS and serum phosphate levels were constant varying from 3.3 to 4 mg/dL during this time period.

The risk of developing neutralising anti-burosumab antibodies is known. So far, no case with clear evidence of lack of efficacy due to anti-Burosumab antibodies has been reported.

2.3.3. Discussion on clinical aspects

X-linked hypophosphatemia (XLH) is a hereditary disease characterized by high levels of circulating fibroblast growth factor 23 (FGF23) that lead to excessive urinary phosphate excretion and subsequent hypophosphataemia.

Crysvita is a fully human monoclonal antibody designed to bind and thereby inhibit the excessive biologic activity of FGF23. In 2018, the European Commission granted a conditional marketing authorization (CMA) for Crysvita for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

The benefits and risks of burosumab in children with XLH were demonstrated in the original MAA based on the ongoing single-arm studies UX023-CL201 and UX023-CL205. As special obligations for a full approval, the MAH committed to complete these studies, as well as the ongoing confirmatory phase 3 Study UX023-CL301. Week 64 data from study UX023-CL301 is currently under assessment in variation (EMEA/H/C/4275/II/04).

The current procedure regards the final report for study UX023-CL201. UX023-CL201 was a randomized, multicentre, open-label, dose-finding Phase 2 study assessed the PD, efficacy, and safety of burosumab in prepubescent children (5 to 12 years old) with XLH.

The study consisted of a 64 week long primary assessment period comparing burosumab dosing every second (Q2W) to dosing every fourth week (Q4W). This was followed by Treatment Extension Period I (Weeks 64 to 160), during which all subjects received burosumab Q2W, aiming to evaluate the long-term safety and efficacy of burosumab. Subjects could choose to end participation in the study at Week 160. For subjects who chose to continue after Week 160, the study also included a Treatment Extension Period II (up to 56 weeks) to provide burosumab treatment to study subjects until the availability of the product. Efficacy data are provided to Week 160.
Methodology and data up to Week 64 were thoroughly assessed in procedure EMEA/H/C/4275 at the original marketing approval for Crysvita and are therefore not repeated here.

The mean burosumab dose per administration was essentially unchanged from Week 64 (1.05 mg/kg for the Q2W group and 1.01 mg/kg for the Q4W group) to Week 190 (1.07 mg/kg).

One hallmark of XLH is low serum phosphate levels due to impaired renal phosphate reabsorption. The beneficial effect of burosumab given Q2W on these pharmacodynamic parameters were maintained from Week 64 to Week 160. P1NP, a marker of bone formation, and CTx, a marker of bone resorption, increased during the study. This is considered to reflect improved bone turnover, which is impaired in XLH. The increase in bone turnover markers was maintained from Week 64.

The primary efficacy endpoint was change from baseline in the Thacher Rickets Severity Score (RSS). Efficacy as determined by RSS was maintained to Week 160, even though the percent change from baseline in the Q2W group was lower at Week 88 and Week 160 compared to Week 40 (-55%, -54% and -61%, respectively). Seven subjects in the Q2W arm were excluded from the Week 160 analysis due to fused or partially fused growth plates.

RSS responder rate was a secondary efficacy endpoint in the study. After Week 64, the RSS responder rate gradually decreased in the Q2W population. A similar development was not seen in the Q4W arm, presumably due to the dose increase to Q2W at Week 64.
In the Q2W arm, responder rate was 80% (16/20) at Week 64, 70% (14/20) at Week 88 and 57% (8/14) (40% [8/20] if adhering to the true ITT population) at Week 160. The population at Week 88 differs slightly from the population at Week 160 as six subjects were excluded from the Week 160 analysis due to fused or partially fused growth plates.

Efficacy of burosumab was also assessed by RGI-C (Radiographic Global Impression of Change) which utilises a 7-point ordinal scale to evaluate the extent of healing in a radiograph as compared with a radiograph taken at a prior time point. The validity of the RGI-C scoring was thoroughly discussed in procedure EMEA/H/C/4275 at the original marketing approval for Crysvita. Efficacy as determined by RGI-C was maintained to Week 160.

Clinical parameters of relevance include growth, 6-minute walking test (6MWT) and subjective scorings.

In the Q2W arm, mean growth velocity was comparable during Week 0-64 and Week 112-160 (6.14 cm/year and 6.12 cm/year, respectively versus 5.45 cm/year at baseline). During Week 64-112, on the other hand, mean growth velocity was lower (5.74 cm/year). It is difficult to find a reasonable explanation for this phenomenon.
Of note, subjects in the Q4W treatment arm do not seem to catch up with the subjects in the Q2W arm in standing height even after transition to the Q2W dosing at Week 64. This supports the chosen posology Q2W.

No further increase in 6MWT distance was seen between Week 88 (+65 m compared to baseline) and Week 160 (+57 m) in the Q2W treatment arm. This is notable. As the mean age per definition increase by 72 weeks, i.e. almost 1.5 years, between Week 88 and Week 160, a longer 6MWT distance at Week 160 would have been expected.

The self-assessment of Functional Disability and Pain according to the POSNA-PODCI scales showed sustained improvement on the Sports/ Physical Functioning, Pain/Comfort, Happiness and global scales up to Week 160.

The spectrum of adverse events reported during the open-label period was in line with previously reported. No new serious adverse event was reported after the CMA of Crysvita. Of note, the frequency of headache events observed in this study (75%) is higher than published reviews of epidemiological studies on headache in children and adolescents, which have found a prevalence of headache in this population of approximately 54% to 58%.

Adverse events of special interest (AESI) include injection site reactions, hyperphosphataemia, ectopic mineralization, dental adverse events and hypersensitivity. These events are all labelled in section 4.4 and/or 4.8 of the Crysvita. No unexpected findings were reported in these areas during the open-label period of the study.

Currently only study results for up to the 64 weeks are described within the SmPC. Section 4.8 and section 5.1 should be updated with data from Study UX023-CL201.

Pre-existing cross-reactive antibodies were present in six subjects at baseline. Three subjects developed neutralising anti-burosumab antibodies during the study. For one subject, presence of neutralising anti-burosumab antibodies was detected more consistently after Week 88 (Weeks 88, 136, 160 and EOS). This subject received 1.5 mg/kg burosumab from Week 54 to EOS and serum phosphate levels were constant varying from 3.3 to 4 mg/dL during this time period.
The risk of developing neutralising anti-burosumab antibodies is known. So far, no case with clear evidence of lack of efficacy due to anti-Burosumab antibodies has been reported.

3. **Overall conclusion and recommendation**

No new and unexpected safety findings were reported during long-term treatment with Crysvita up to a maximum of 214 weeks. The beneficial effects of Crysvita were maintained during the open-label extension period. The benefit/risk ratio of Crysvita is considered unchanged.

The final report of Study UX023-CL201 fulfils Special obligation number 1 for Crysvita.

The MAH does not propose any updates to the Product information at this time point. This is not fully agreed, as Annex II of the Product information needs to be varied to reflect the fact that Special obligation number 1 is considered fulfilled. An appropriate variation should be submitted accordingly. Furthermore, the long-term data from study UX023-CL201 should be added to section 5.1 of the SmPC. Likewise, section 4.8 should be amended reflecting new frequencies of adverse events based on this study. However, if the MAH prefers to await the results from the two studies comprising the additional Special obligations and update section 4.8 and 5.1 with results from all three studies at the same time, this is considered acceptable.

☒ **Fulfilled:**

No further action required. However, as the Special obligation number 1 is considered fulfilled, this condition should be removed from Annex II in the Product information. A variation should be submitted. The RMP should be updated accordingly at the next procedure involving the RMP.

Amendment of sections 4.8 and 5.1 with results from study UX023-CL201 could be done in a later Type II variation when results from the two studies comprising the additional Special obligations are present, if the MAH prefers that.

4. Additional clarification requested

Not Applicable