CRYSVITA® Solution for Injection
Burosumab

1. NAME OF THE MEDICINAL PRODUCT

CRYSVITA 10 mg solution for injection
CRYSVITA 20 mg solution for injection
CRYSVITA 30 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CRYSVITA 10 mg solution for injection
Each vial contains 10 mg of burosumab in 1 ml solution.

CRYSVITA 20 mg solution for injection

Each vial contains 20 mg of burosumab in 1 ml solution.

CRYSVITA 30 mg solution for injection

Each vial contains 30 mg of burosumab in 1 ml solution.

Burosumab is a recombinant human monoclonal IgG1 antibody for FGF23 and is produced by recombinant DNA technology using Chinese hamster ovary (CHO) mammalian cell culture.

Excipient with known effect
Each vial contains 45.91 mg sorbitol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear to slightly opalescent, colorless to pale brownish-yellowish solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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.

4.2. Posology and method of administration

Treatment should be initiated by a physician experienced in the management of patients with metabolic bone diseases.

Posology

Oral phosphate and active vitamin D analogues (e.g. calcitriol) must be discontinued 1 week prior to initiation of treatment. As burosumab however increases active vitamin D synthesis (see section 5.1), patients' requirements for replacement or supplementation with inactive vitamin D should be assessed. Vitamin D replacement or supplementation with inactive forms may be started or continued as per local guidelines under monitoring of

serum calcium and phosphate. At initiation, fasting serum phosphate level should be below the reference range for age (see section 4.3).

Serum calcium concentration should be monitored before initiation of treatment, and 1-2 weeks after initiation and dose adjustments in addition to regular monitoring during treatment (see section 4.4).

Dosing in Children and Adolescents aged 1 to 17 years

The recommended starting dose in children and adolescents aged 1 to 17 years is 0.8 mg/kg of body weight given every two weeks. Doses should be rounded to the nearest 10 mg. The maximum dose is 90 mg.

Fasting serum phosphate should be monitored as appropriate during treatment with burosumab, including after any dose adjustment, to ensure that it remains within the reference range for age. Blood samples for measurement of serum phosphate must always be obtained approximately 2 weeks post dose.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. If fasting serum phosphate is within the reference range for age, the same dose should be maintained.

If fasting serum phosphate is not within the reference range, dose adjustment (dose increase/dose decrease) may be required (see below). Fasting serum phosphate should be re-measured 4 weeks after any dose adjustment. If fasting serum phosphate is within reference range at remeasurement, the new dose should be maintained, otherwise further dose adjustment should be considered.

Dose increase

If fasting serum phosphate is below the reference range for age, the dose may be increased stepwise by 0.4 mg/kg up to a maximum dose of 2.0 mg/kg (maximum dose of 90 mg). Fasting serum phosphate should be measured 4 weeks after dose adjustment. Burosumab should not be adjusted more frequently than every 4 weeks.

Dose decrease

If fasting serum phosphate is above the reference range for age, the next dose should be withheld and the fasting serum phosphate reassessed within 2 weeks. The patient must have fasting serum phosphate below the reference range for age to restart burosumab at half of the previous dose, rounding the amount as described above. If the level remains below the reference range after the first re-initiation dose, the dose can be increased as described under “Dose increase” (above).

Dose Conversion at age 18 years

Children and adolescents aged 1 to 17 years should be treated using the dosing guidance outlined above. At 18 years of age the patient should convert to the adult dose and dosing regimen as outlined below.

Dosing in Adults

The recommended starting dose in adults is 1.0 mg/kg of body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, given every 4 weeks.

After initiation of treatment with burosumab, fasting serum phosphate should be measured every 2 weeks for the first month of treatment, every 4 weeks for the following 2 months and thereafter as appropriate. Fasting serum phosphate should be measured 2 weeks after the previous dose of burosumab. If serum phosphate is within the normal range, the same dose should be continued.

Dose decrease
If serum phosphate is above the upper limit of normal range, the next dose should be withheld and the serum phosphate level reassessed within 2 weeks. The patient must have serum phosphate below the normal range before restarting burosumab. Once serum phosphate is below the normal range, treatment may be restarted at half the initial starting dose up to a maximum dose of 40 mg every 4 weeks. Serum phosphate should be reassessed 2 weeks after any change in dose.

If the level remains below the reference range after the first re-initiation dose, the dose can be increased at the discretion of the physician in increments up to 1.0 mg/kg, rounded to the nearest 10 mg (to a maximum (total) administration dose of 90 mg), administered every 4 weeks. Serum phosphate levels should be reassessed 2 weeks after dose adjustment.

All Patients
To decrease the risk for ectopic mineralization, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range (see section 4.4).

Missed dose
Treatments may be administered 3 days either side of the scheduled treatment date if needed for practical reasons. If a patient misses a dose, burosumab should be resumed as soon as possible at the prescribed dose.

Special populations

Renal impairment
No or limited data are available in patients with renal impairment. Burosumab must not be given to patients with severe or end stage renal disease (see section 4.3).

Pediatric population
The safety and efficacy of burosumab in children aged less than one year have not been established in clinical studies.

Elderly
Limited data is available in patients over 65 years of age.

Method of administration
For subcutaneous use.

Burosumab should be injected in the upper arm, abdomen, buttock or thigh.

The maximum volume of medicinal product per injection site is 1.5 ml. If more than 1.5 ml is required on a given dosing day, the total volume of medicinal product must be split and administered at two or more different injection sites. Injection sites should be rotated and carefully monitored for signs of potential reactions (see section 4.4).

For handling of burosumab before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concurrent administration with oral phosphate, active vitamin D analogs (see section 4.5).

Fasting serum phosphate above the normal range for age due to the risk of hyperphosphatemia (see section 4.4).

Patients with severe renal impairment or end stage renal disease.

4.4. Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded within the patient's records.

Ectopic mineralization
Ectopic mineralization, as manifested by nephrocalcinosis, has been observed in patients with XLH treated with oral phosphate and active vitamin D analogs; these medicinal products should be stopped at least 1 week prior to initiating burosumab treatment (see section 4.2).

Monitoring for signs and symptoms of nephrocalcinosis, e.g. by renal ultrasonography, is recommended at the start of treatment and every 6 months for the first 12 months of treatment, and annually thereafter. Monitoring of plasma alkaline phosphatase, calcium, parathyroid hormone (PTH) and creatinine is recommended every 6 months (every 3 months for children 1 - 2 years) or as indicated.

Monitoring of urine calcium and phosphate is suggested every 3 months.

Hyperphosphataemia
Levels of fasting serum phosphate should be monitored due to the risk of hyperphosphatemia. To decrease the risk for ectopic mineralization, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range for age. Dose interruption and/or dose reduction may be required (see section 4.2). Periodic measurement of post prandial serum phosphate is advised.

Hypercalcaemia and hyperparathyroidism
Increases in serum calcium or parathyroid hormone have been reported in patients treated with burosumab. Factors such as hyperparathyroidism, prolonged immobilisation, dehydration, hypervitaminosis D or renal impairment may increase the risk of hypercalcaemia. In particular, severe hypercalcaemia has been reported in subjects with tertiary hyperparathyroidism. Serum calcium and parathyroid hormone levels should be monitored before and during burosumab treatment (see section 4.2). In patients with moderate to severe hypercalcaemia (>3 mmol/l), burosumab should not be administered until hypercalcaemia is adequately treated.

Injection site reactions
Administration of burosumab may result in local injection site reactions. Administration should be interrupted in any patient experiencing severe injection site reactions (see section 4.8) and appropriate medical therapy administered.

Hypersensitivity
Therapeutic proteins, such as burosumab, may be associated with hypersensitivity reactions. In Clinical Studies, mild or moderate hypersensitivity reactions (e.g., rash, injection site rash) were observed (see section 4.8). Burosumab must be discontinued if serious hypersensitivity reactions occur and appropriate medical treatment should be initiated.

Excipient with known effect
This medicine contains 45.91 mg of sorbitol in each vial which is equivalent to 45.91 mg/ml. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

This medicine contains 0.5 mg of polysorbate 80 in each vial which is equivalent to 0.5 mg/ml. Polysorbates may cause allergic reactions.

4.5. Interaction with other medicinal products and other forms of interaction

Concurrent administration of burosumab with oral phosphate and active vitamin D analogs is contraindicated as it may cause an increased risk of hyperphosphatemia and hypercalcaemia (see section 4.3).

Caution should be exercised when combining burosumab with calcimimetic medicinal products (i.e. agents that mimic the effect of calcium on tissues by activating the calcium receptor). Co-administration of these medicinal products has not been studied in clinical trials, therefore close monitoring of serum calcium levels is recommended (see section 4.4).

4.6. Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective contraception during treatment with burosumab and for at least 14 weeks after stopping treatment.

Pregnancy
There are no or limited amount of data from the use of burosumab in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Burosumab is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether burosumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to low concentrations soon afterwards. Consequently a risk to the breast-fed newborn cannot be excluded during this short period. Afterwards, use of burosumab could be considered during breast-feeding only if clinically needed.

Fertility
Studies in animals have shown effects on male reproductive organs (see section 5.3). There are no clinical data available on the effect of burosumab on human fertility. No specific fertility studies in animals with burosumab were conducted.

4.7. Effects on ability to drive and use machines

Burosumab has a minor influence on the ability to drive and use machines. Dizziness may occur following administration of burosumab.

4.8. Undesirable effects

Summary of the safety profile
The most common (>10%) adverse drug reactions reported in pediatric patients treated for up to 64 weeks during clinical trials were: injection site reactions (56%), cough (56%), headache (50%), pyrexia (43%), pain in extremity (40%), vomiting (39%), tooth abscess (35%), vitamin D decreased (32%), diarrhea (25%), rash (24%), nausea (15%), constipation (11%), dental caries (11%) and myalgia (11%).

The most common adverse drug reactions reported in adult patients during clinical trials were: back pain (23%), headache (21%), tooth infection (19%), restless legs syndrome (13%), muscle spasms (12%), vitamin D decrease (15%) and dizziness (11%). (See section 4.4 and ‘Description of selected adverse reactions’ below).

Tabulated list of adverse reactions
The adverse reactions are presented by system organ class and frequency categories,

defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

An overview of adverse reactions observed from clinical trials and post-marketing in pediatric patients is presented in Table 1.

Table 1: Adverse reactions reported in pediatric patients >1 to 17 years of age with XLH, observed from clinical trials (N=120) and post-marketing

MedDRA System Organ Class	Frequency category	Adverse reaction
Infections and infestations	Very common	Tooth abscess [1]
Endocrine disorders	Not known	Hyperparathyroidism[2] (see section 4.4)
Metabolism and nutrition disorders	Uncommon	Hypercalcaemia[3,4] (see section 4.4)
	Not known	Hypercalciuria[5]
Respiratory, thoracic and mediastinal disorders	Very common	Cough [6]
Nervous system disorders	Very common	Headache
	Common	Dizziness [7]
Gastrointestinal Disorders	Very common	Vomiting Nausea Diarrhea Constipation Dental Caries
Skin and subcutaneous tissue disorders	Very common	Rash [8]
	Common	Urticaria[4]
Musculoskeletal and connective tissue disorders	Very common	Myalgia Pain in extremity
General disorders and administration site conditions	Very common	Injection site reaction [9] Pyrexia
Investigations	Very common	Vitamin D decreased [10]
	Common	Blood parathyroid hormone increased (see section 4.4)[4]
	Not known	Blood phosphorus increased [11]

1 Tooth abscess includes: *Tooth abscess, Tooth infection and Toothache*

2 Hyperparathyroidism includes: *Hyperparathyroidism, Hyperparathyroidism secondary and Hyperparathyroidism tertiary*

3 Hypercalcaemia includes: *Hypercalcaemia and Blood calcium increased*

4 Seen in clinical trials, confirmed by post-marketing experience

5 Hypercalciuria includes: *Hypercalciuria and Urine calcium increased*

6 Cough includes: *Cough, and Productive cough*

7 Dizziness includes: *Dizziness, and Dizziness exertional*

8 Rash includes: *Rash, Rash erythematous, Rash generalized, Rash pruritic, Rash maculo-papular, and Rash pustular*

9 Injection site reaction includes: *Injection site reaction, Injection site erythema, Injection*

site pruritus, Injection site swelling, Injection site pain, Injection site rash, Injection site bruising, Injection site discoloration, Injection site discomfort, Injection site haematoma, Injection site hemorrhage, Injection site induration, Injection site macule, and Injection site urticaria

10 Vitamin D decreased includes: *Vitamin D deficiency, Blood 25-hydroxycholecalciferol decreased, and* Vitamin D decreased

11 Blood phosphorus increased includes: *Blood phosphorus increased and Hyperphosphataemia*

An overview of adverse reactions observed from clinical trials in adults is presented in Table 2.

Table 2: Adverse reactions reported in adults with XLH (N=176) and post-marketing

MedDRA System Organ Class	Frequency Category	Adverse Reaction
Infections and infestations	Very common	Tooth infection[1]
Endocrine disorders	Common	Hyperparathyroidism[2,3] (see section 4.4)
Metabolism and nutrition disorders	Common	Hypercalciuria[4]
	Not known	Hypercalcaemia[5] (see section 4.4)
Nervous system disorders	Very common	Headache[6]
	Very common	Dizziness
	Very common	Restless legs syndrome
Gastrointestinal disorders	Common	Constipation
Skin and subcutaneous tissue disorders	Common	Urticaria[3]
Musculoskeletal and connective tissue disorders	Very common	Back pain
	Very common	Muscle spasms
General disorders and administration site conditions	Very common	Injection site reaction[7]
Investigations	Very common	Vitamin D decreased[8]
	Common	Blood phosphorus increased[9] Blood parathyroid hormone increased[3] (see section 4.4)

1 Tooth infection includes: *Tooth abscess,tooth infection and toothache*

2 Hyperparathyroidism includes: *Hyperparathyroidism, Hyperparathyroidism secondary and Hyperparathyroidism tertiary*

3 Seen in clinical trials, confirmed by post-marketing experience

4 Hypercalciuria includes: *Hypercalciuria and Urine calcium increased*

5 Hypercalcaemia includes: *Hypercalcaemia and Blood calcium increased*

6 Headache includes: *Headache and Head discomfort*

7 Injection site reaction includes: I*njection 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, Injection site urticaria, Injection site hypersensitivity and Injection site inflammation*

[8] Vitamin D decreased includes: *Vitamin D deficiency, Blood 25-hydroxycholecalciferol decreased, and Vitamin D decreased*

[9] Blood phosphorus increased includes: *Blood phosphorus increased, and Hyperphosphataemia*

Description of selected adverse reactions

Injection site reactions
Pediatric patients:
Local reactions (e.g. injection site urticaria, erythema, rash, swelling, bruising, pain, pruritus, and haematoma) have occurred at the site of injection. In the pediatric studies, approximately 56% of the patients had an injection site reaction. The injection site reactions were generally mild in severity, occurred within 1 day of medicinal product administration, lasted approximately 1 to 3 days, required no treatment, and resolved in almost all instances.

Adult patients:
The frequency of injection site reactions was 12% in both burosumab and placebo treatment groups (injection site reaction, erythema, rash, bruising, pain, pruritis and haematoma). The injection site reactions were generally mild in severity, occurred within 1 day of medicinal product injection, lasted approximately 1 to 3 days, required no treatment, and resolved in almost all instances.

Hypersensitivity
Pediatric patients:
Hypersensitivity reactions (including: injection site rash, rash, urticaria, swelling face, dermatitis) were reported in 18% of pediatric patients. All reported reactions were mild or moderate in severity.

Adult patients:
The incidence of potential hypersensitivity reactions was similar (6%) in the burosumab treated and placebo treated adults. The events were mild to moderate in severity.

Vitamin D Decreased
Pediatric patients:
Reduced serum 25 hydroxy-vitamin D has been observed following initiation of burosumab treatment in approximately 8% of pediatric patients, possibly due to increased conversion to activated 1,25 dihydroxy-Vitamin D. Supplementation with inactive vitamin D was successful in restoring plasma levels to normal.

Hyperphosphataemia
Adult patients:
In the double-blind period of Study UX023-CL303, in the burosumab group during the Placebo-controlled Treatment Period, 9 subjects (13.2%) had high serum phosphate at least once; 5 of these 9 required protocol-specified dose reduction(s). After initiation of burosumab in the open-label Treatment Continuation Period, 8 subjects (12.1%) in the placebo→burosumab group had high serum phosphate levels. Four of these 8 subjects required protocol-specified dose reduction(s). The dose for all patients meeting the protocol-specified criteria was reduced by 50%. A single patient (1%) required a second dose reduction for continued hyperphosphataemia.

Restless legs syndrome
Adult patients:
In adults, approximately 12% of the burosumab treatment group and 8% in the placebo group had a worsening of baseline restless legs syndrome or new onset restless legs syndrome of mild to moderate severity.

Immunogenicity:
Pediatric and adult patients
Overall, the incidence of anti-drug antibodies (ADA) to burosumab was <10% in adults and pediatric subjects administered burosumab. The incidence of neutralizing ADA was 3.2% and neutralizing ADA were only found in pediatric subjects. No adverse events, loss of efficacy, or changes in pharmacokinetics profile were associated with these findings.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9. Overdose

There is no experience with overdose of burosumab. Burosumab has been administered in pediatric clinical trials without dose limiting toxicity using doses up to 2.0 mg/kg body weight with a maximal dose of 90 mg every two weeks. In adult clinical trials no dose limiting toxicity has been observed using doses up to 1.0 mg/kg or a maximal total dose of 128 mg every 4 weeks.

Management
In case of overdose, it is recommended to stop burosumab and to monitor biochemical response.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of bone diseases, other drugs affecting bone structure and mineralization, ATC code: M05BX05.

Mechanism of action
Burosumab is a recombinant human monoclonal antibody (IgG1) that binds to and inhibits the activity of fibroblast growth factor 23 (FGF23). By inhibiting FGF23, burosumab increases tubular reabsorption of phosphate from the kidney and increases serum concentration of 1,25 dihydroxy-Vitamin D.

Clinical efficacy in pediatric patients with XLH

Study UX-023-CL301
In pediatric study UX023-CL301 61 patients aged 1 to 12 years (56% female; 44% male, Age at first dose, mean (SD): 6.3 (3.31) years) were randomized to burosumab (n=29) or active control (n=32; oral phosphate and active vitamin D). At entry to the study all patients had to have had a minimum of 6 months treatment of oral phosphate and active vitamin D. All patients had radiographic evidence of bone disease due to XLH (Rickets severity score ≥2). Burosumab was started at a dose of 0.8 mg/kg every 2 weeks and increased to 1.2 mg/kg if there was inadequate response, as measured by fasting serum phosphate. Those patients randomized to active control group received multiple daily doses of oral phosphate and active vitamin D.

The primary efficacy endpoint was the change in severity of rickets at Week 40, as assessed by the RGI-C (Radiographic Global Impression of change) score, compared between the burosumab and active control groups.

The RGI-C is a relative rating scale that compares a patient's rickets before and after treatment utilizing a 7-point ordinal scale to evaluate change in the same abnormalities rated in the RSS (as described below). Scores range from -3 (indicating severe worsening

of rickets) to +3 (indicating complete healing of rickets).

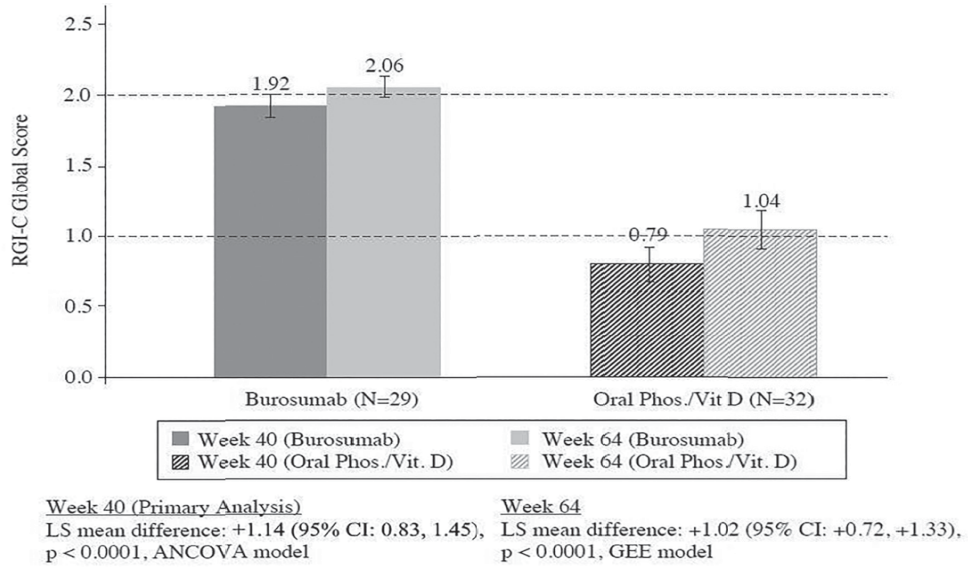
The severity of pediatric rickets was measured using the RSS, a radiographic scoring method based on the degree of metaphyseal fraying, concavity, and the proportion of the growth plate affected. In the UX023-CL301 study, the RSS was scored using a predefined scale looking at specific abnormalities in the wrists and knees.

All patients completed at least 64 weeks of randomized treatment, no patients had dose reductions and 8 (28%) of burosumab-treated patients received dose escalations to 1.2 mg/kg.

Primary Efficacy Results

Greater healing of rickets at Week 40 was seen with burosumab treatment compared to active control and this effect was maintained at week 64, as shown in Figure 1.

Figure 1: RGI-C Global Score (Mean ± SE) – Primary Efficacy Endpoint at Week 40 and 64 (Full Analysis Set)



Week 40 (Primary Analysis)
LS mean difference: +1.14 (95% CI: 0.83, 1.45), p < 0.0001, ANCOVA model

Week 64
LS mean difference: +1.02 (95% CI: +0.72, +1.33), p < 0.0001, GEE model

Secondary Efficacy Results

Key Secondary efficacy endpoint results are presented in Table 3.

Table 3: Secondary Efficacy Endpoint Results

Endpoint	**Week**	**Active Control** LS Mean (SE)	**Burosumab** LS Mean (SE)	**Difference** (burosumab – active control)
Lower Limb Deformity; assessed by RGI-C (GEE model)	40	+0.22 (0.080)	+0.62 (0.153)	+0.40 [95% CI: 0.07, 0.72] p = 0.0162
	64	+0.29 (0.119)	+1.25 (0.170)	+0.97 [95% CI: +0.57, +1.37] p < 0.0001
Height; Z-score	Baseline	-2.05 (0.87)	-2.32 (1.17)	
	40 [a]	+0.03 (0.031)	+0.16 (0.052)	+0.12 [95% CI: 0.01, 0.24] p = 0.0408
	64 [b]	+0.02 (0.035)	+0.17 (0.066)	+0.14 [95% CI: 0.00, 0.29] p = 0.0490

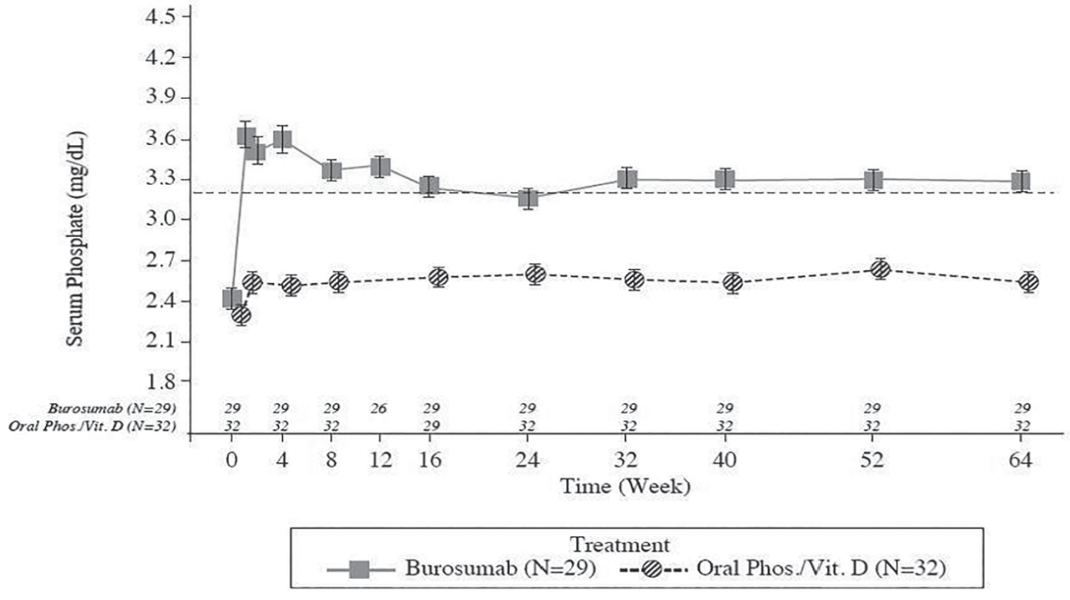
Rickets severity, RSS total Score	Baseline	3.19 (1.141)	3.17 (0.975)	
	40 [a]	-0.72 (0.162)	-2.08 (0.104)	-1.34 [95% CI: 1.74, -0.94] p < 0.0001
	64 [b]	-1.01 (0.151)	-2.23 (0.117)	-1.21 [95% CI: -1.59, -0.83] p < 0.0001
Serum ALP (U/L)	Baseline	523 (154)	511 (125)	
	40 [a]	489 (189)	381 (99)	-97 [95% CI: -138, -56] p < 0.0001
	64 [b]	495 (182)	337 (86)	-147 [95% CI: -192, -102] p < 0.0001
Six Minute Walk Test (m)	Baseline	450 (106)	385 (86)	
	40 [a]	+4 (14)	+47 (16)	+43 [95% CI: -0.3, 87] p = 0.0514
	64 [b]	+29 (17)	+75 (13)	+46 [95% CI: 2, 89] p = 0.0399

[a:] the change from Baseline to Week 40 from ANCOVA model.
[b:] the change from Baseline to Week 64 from GEE Model.

Serum Phosphate
At each study visit at which serum phosphate was assessed in both groups, changes in serum phosphate from Baseline were larger in the burosumab group compared with the active control group (p < 0.0001; GEE model) (Figure 2).

Figure 2: Serum Phosphate Concentration and Change from Baseline (mg/dL) (Mean ± SE) by Treatment Group (PD Analysis Set)

Note: Dashed line in figure indicates the lower limit of the normal serum phosphate reference range, 3.2 mg/ dL (1.03 mmol/L)



Study UX023-CL201
In pediatric Study UX023-CL201, 52 pediatric patients aged 5 to 12 years (mean 8.5 years; SD 1.87) with XLH were treated for 64 weeks. Nearly all patients had radiographic evidence of rickets at baseline and had received prior oral phosphate and vitamin D analogs for a mean (SD) duration of 7 (2.4) years. This conventional therapy was discontinued 2-4 weeks prior to burosumab initiation. The burosumab dose was adjusted to target a fasting serum phosphate concentration of 3.50 to 5.02 mg/dL (1.13 to 1.62 mmol/L). Twenty six of 52 patients received burosumab every 4 weeks (Q4W). Twenty six of 52 patients received burosumab every two weeks (Q2W) at an average dose (min, max) of 0.73 (0.3, 1.5), 0.98 (0.4, 2.0) and 1.04 (0.4, 2.0) mg/kg at weeks 16, 40 and 60 respectively, and up to a maximum dose of 2.0 mg/kg.

Burosumab increased serum phosphate concentration and increased TmP/GFR. In the group that received burosumab every 2 weeks, mean (SD) serum phosphate concentration increased from 2.38 (0.405) mg/dL (0.77 (0.131) mmol/L) at baseline), to 3.3 (0.396) mg/dL (1.07 (0.128) mmol/L) at Week 40 and was maintained to Week 64 at 3.35 (0.445) mg/dL (1.08 (0.144) mmol/L).

Alkaline phosphatase activity
Mean (SD) serum total alkaline phosphatase activity was 459 (105) U/L at baseline and decreased to 369 (76) U/L at Week 64 (-19.6%, $p < 0.0001$).

Bone-derived serum alkaline phosphatase content was 165 (52) µg/L [mean (SD)] at Baseline and 115 (31) µg/L at Week 64 (mean change: -28.5%).

The severity of pediatric rickets in Study UX023-CL201 was measured using the RSS, as described above. In Study UX023-CL201, the RSS was scored using a predefined scale looking at specific abnormalities in the wrists and knees. As a complement to the RSS assessment, the RGI-C rating scale was used. Results are summarized in Table 4.

Table 4: Rickets Response in Children 5-12 Years Receiving Burosumab in Study UX023-CL201

Endpoint	Duration of Burosumab (week)	Effect Size	
		Q2W (N=26)	Q4W (N=26)
RSS Total Score			
Baseline Mean (SD)		1.92 (1.2)	1.67 (1.0)
LS Mean change (SE) from baseline in total score[a] (reduced RSS score indicates improvement in rickets severity)	40	-1.06 (0.1) (p<0.0001)	-0.73 (0.1) (p<0.0001)
	64	-1.00 (0.1) (p<0.0001)	-0.84 (0.1) (p<0.0001)
RGI-C Global Score			
LS Mean score (SE) [a] (positive indicates healing)	40	+1.66 (0.1) (p<0.0001)	+1.47 (0.1) (p<0.0001)
	64	+1.56 (0.1) (p<0.0001)	+1.58 (0.1) (p<0.0001)

[a)] The estimates of LS means and p-values are from the generalized estimation equation model accounting for baseline RSS, visits and regimen and its interaction.

Study UX023-CL205
In pediatric Study UX023-CL205, burosumab was evaluated in 13 XLH patients, aged 1 to 4 years (mean 2.9 years; SD 1.1) for 40 weeks. All patients had radiographic evidence of rickets at baseline and twelve patients had received oral phosphate and vitamin D analogs for a mean (SD) duration of 16.7 (14.4) months. This conventional

therapy was discontinued 2-6 weeks prior burosumab initiation. Patients received burosumab at a dose of 0.8 mg/kg every two weeks.

In Study UX023-CL205, mean (SD) fasting serum phosphate concentration increased from 2.51 (0.284) mg/dL (0.81 (0.092) mmol/L) at baseline to 3.47 (0.485) mg/dL (1.12 (0.158) mmol/L) at Week 40.

Serum alkaline phosphatase activity
Mean (SD) serum total alkaline phosphatase activity was 549 (193.8) U/L at baseline and decreased to 335 (87.6) U/L at Week 40 (mean change: -36.3%).

Rickets Severity Score (RSS)
After 40 weeks of treatment with burosumab, mean total RSS improved from 2.92 (1.367) at baseline to 1.19 (0.522), corresponding to a change from baseline in LS mean (SE) change of -1.73 (0.132) ($p<0.0001$).

Radiographic Global Impression of Change (RGI-C)
After 40 weeks of treatment with burosumab, the LS mean (SE) RGI-C Global score was +2.33 (0.08) in all 13 patients ($p < 0.0001$) demonstrating healing of rickets. All 13 patients were considered RGI-C responders as defined by RGI-C global score ≥ +2.0.

Clinical efficacy in adults with XLH

Study UX023-CL303
Study UX023-CL303 is a randomized, double-blind, placebo-controlled study in 134 adult XLH patients. The study comprised of a 24-week placebo-controlled treatment phase followed by a 24-week open-label period where all patients received burosumab. Oral phosphate and active vitamin D analogs were not allowed during the study. Burosumab was administered at a dose of 1 mg/kg every 4 weeks. The primary endpoint of this study was normalization of serum phosphate across the 24-week double-blind period. Key secondary endpoints included worst pain as measured by the Brief Pain Inventory (BPI) scale and stiffness and physical function as measured by the WOMAC (Western Ontario and McMaster Universities Osteoarthritis) Index. Exploratory endpoints included fracture and pseudofracture healing, enthesopathy, 6 Minute Walk Test, BPI Pain interference, Brief Fatigue Inventory (BFI) worst fatigue and BFI global fatigue score.

At study entry, the mean age of patients was 40 years (range 19 to 66 years) and 35% were male. 66 patients were randomized to placebo treatment and 68 to burosumab treatment; at baseline, mean (SD) serum phosphate was 0.62 (0.10) mmol/L [1.92 (0.32) mg/dL] and 0.66 (0.1 mmol/L) [2.03 (0.30) mg/dL] in the placebo and burosumab groups respectively.

For the primary efficacy endpoint, a greater proportion of patients treated with burosumab achieved a mean serum phosphate level above the lower limit of normal (LLN) compared to the placebo group through week 24 (Table 5 and Figure 3).

Table 5: Proportion of Adult Patients Achieving Mean Serum Phosphate Levels Above the LLN at the Midpoint of the Dose Interval in Study UX023-CL303 (Double-Blind Period)

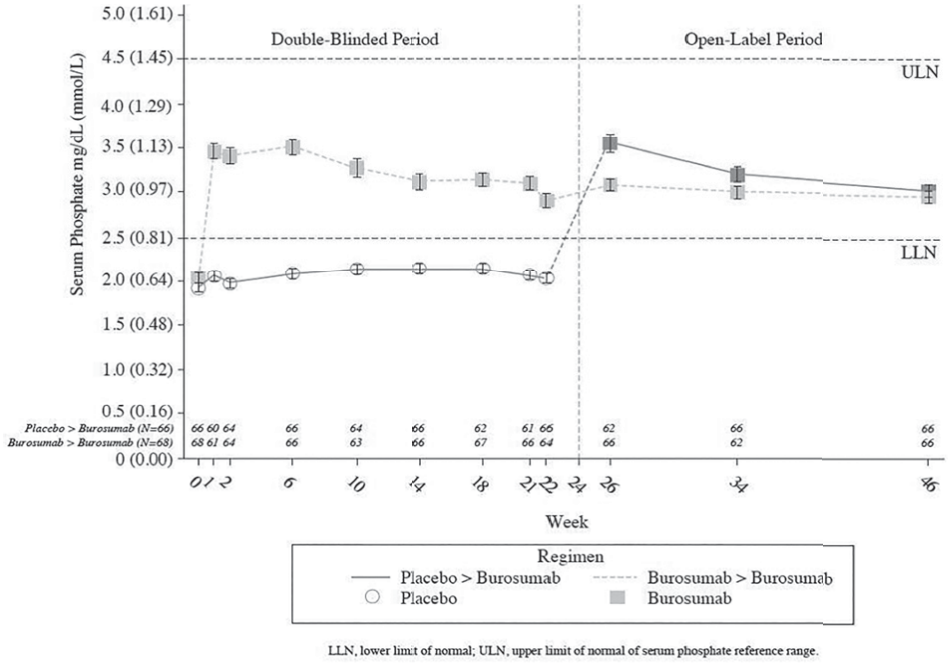
	Placebo (N = 66)	**Burosumab (N = 68)**
Achieved Mean Serum Phosphate > LLN Across Midpoints of Dose Intervals Through Week 24 - n (%)	7.6% (5/66)	94.1% (64/68)

95% CI	(3.3, 16.5)	(85.8, 97.7)
p- value[a]		<0.0001

The 95% CIs are calculated using the Wilson score method

[a] P-value is from Cochran-Mantel-Haenszel (CMH) testing for association between achieving the primary endpoint and treatment group, adjusting for randomization stratifications.

Figure 3: Mean (± SE) Serum Phosphate Peak Concentrations (mg/dL [mmol/L])



LLN, lower limit of normal; ULN, upper limit of normal of serum phosphate reference range.

Patient reported pain, physical function and stiffness

Change from baseline at Week 24 showed a larger difference for burosumab relative to placebo in patient reported pain (BPI), physical function (WOMAC Index) and stiffness (WOMAC Index). The mean (SE) difference between treatment groups (burosumab-placebo) reach statistical significance for WOMAC stiffness at Week 24. Details are shown in Table 6.

Table 6: Patient reported pain, physical function and stiffness score changes from baseline to Week 24 and analysis of difference at Week 24

	Placebo	**Burosumab**
	N=66	N=68
BPI worst pain [a]		
LS Mean (SE) change from Baseline	-0.32 (0.2)	-0.79 (0.2)
[95% CIs]	[-0.76, 0.11]	[-1.20, -0.37]

LS Mean (SE) Difference (Burosumab-Placebo)	-0.5 (0.28)	
p-value	0.0919 [c]	
WOMAC Index physical function [b]		
LS Mean (SE) change from Baseline	+1.79 (2.7)	-3.11 (2.6)
[95% CIs]	[-3.54, 7.13]	[-8.12,1.89]
LS Mean (SE) Difference	-4.9 (2.5)	
p-value	0.0478 [c]	
WOMAC Index stiffness [b]		

	Placebo	**Burosumab**
LS Mean (SE) change from Baseline	+0.25 (3.1)	-7.87 (3.0)
[95% CIs]	[5.89, 6.39]	[-13.82, 1.91]
LS Mean (SE) Difference (Burosumab-Placebo)	-8.12 (3.2)	
p-value	0.0122	

[a] BPI worst pain item score ranges from 0 (no pain) to 10 (pain as bad as you can imagine)

[b] WOMAC Index physical function and stiffness domains range from 0 (best health) to 100 (worst health)

[c] Not significant following Hochberg adjustment

6 Minute Walk Test

This exercise test was conducted in all patients at Baseline, Week 12, 24, 36 and 48 (LS mean difference in change from baseline, burosumab → placebo; Table 7). Improvements continued through to Week 48 where distance walked increased from 357 m at baseline to 393 m at Week 48. Patients who crossed over from placebo to burosumab achieved similar improvements after 24 weeks of treatment.

Table 7: 6 Minute Walk distance (SD) Baseline and Week 24; Least Squares Mean Difference (SE)

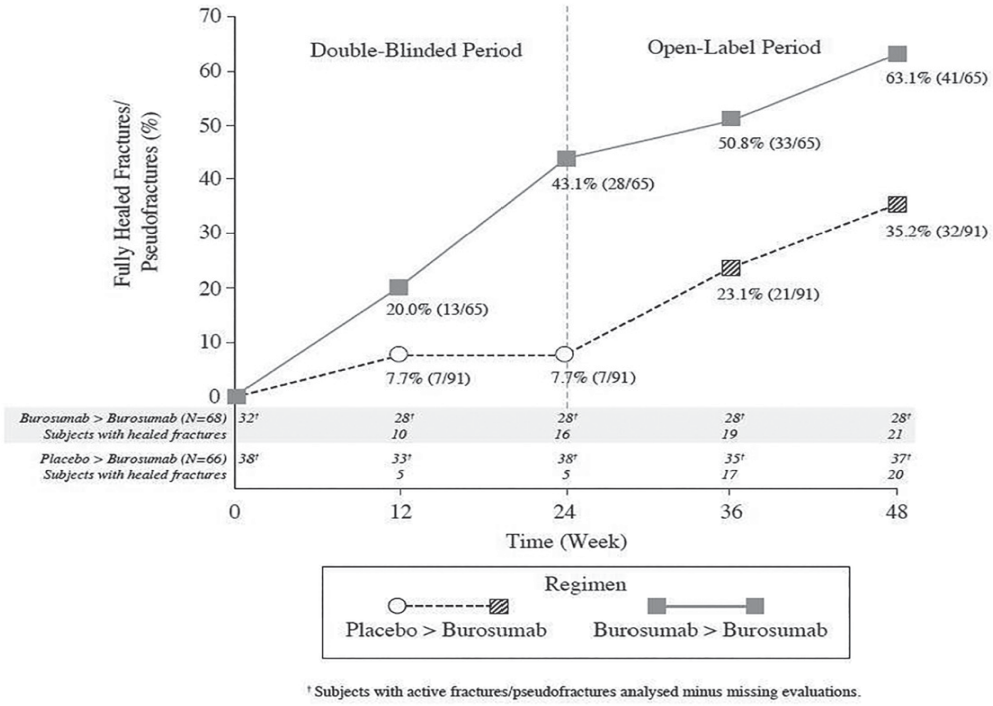
6 MWT, m(SD)	**Placebo**	**Burosumab**
Baseline	367 (103)	357 (109)
Week 24	369 (103)	382 (108)
LS Mean difference burosumab-placebo (SE)	20 (7.7)	

Radiographic Evaluation of Fractures and Pseudofractures

In Study UX023-CL303, a skeletal survey was conducted at baseline to identify osteomalacia-related fractures and pseudofractures. There were 52% (70/134) of patients who had either active fractures (12%, 16/134) or active pseudofractures (47%, 63/134) at baseline. Following burosumab treatment more patients showed healing of fractures and pseudofractures compared to the placebo group (Figure 4). During the placebo-controlled treatment period up to week 24, a total of 6 new fractures or pseudofractures appeared in 68 patients receiving burosumab compared to 8 new

abnormalities in 66 patients receiving placebo. Of the number of new fractures developed prior to week 48 most (10/18) were healed or partially healed at the end of the study.

Figure 4: Percentage of Healed Active Fractures and Pseudofractures in Study UX023-CL303



† Subjects with active fractures/pseudofractures analysed minus missing evaluations.

At Baseline, the mean (SD) total calcaneal enthesopathy burden (sum of superior and inferior calcaneal spurs) was 5.64 (3.12) cm in the burosumab group and 5.54 (3.1) cm in the placebo group. At Week 24, the mean (SD) total calcaneal enthesopathy burden was 5.90 (3.56) cm in the burosumab→burosumab group and 4.07 (2.38) cm in the placebo→burosumab group.

For the exploratory endpoints of BPI Pain interference, BFI worst fatigue and BFI global fatigue score no meaningful difference were observed between treatment arms.

Bone Histomorphometry in Adults

Study UX023-CL304

Study UX023-CL304 is a 48-week, open-label, single-arm study in adult XLH patients to assess the effects of burosumab on improvement of osteomalacia as determined by histologic and histomorphometric evaluation of iliac crest bone biopsies. Patients received 1.0 mg/kg burosumab every 4 weeks. Oral phosphate and active vitamin D analogs were not allowed during the study.

14 patients were enrolled, and at study entry, the mean age of patients was 40 years (range 25 to 52 years) and 43% were male. After 48 weeks of treatment in Study UX023-CL304 paired biopsies were available from 11 patients; healing of osteomalacia was observed in all ten evaluable patients as demonstrated by decreases in osteoid volume/bone volume (OV/BV) from a mean (SD) score of 26.1% (12.4) at baseline to 11.9% (6.6), Osteoid thickness (O.Th) declined in 11 evaluable patients from a mean (SD) of 17.2 (4.1) micrometers to 11.6 (3.1) micrometers.

5.2. Pharmacokinetic properties

Absorption

Burosumab absorption from subcutaneous injection sites to blood circulation is nearly complete. Following subcutaneous administration, the median time to reach maximum serum concentrations (T_{max}) of burosumab is approximately 7-13 days. The peak serum concentration (C_{max}) and area under the concentration-time curve (AUC) of serum burosumab is dose proportional over the dose range of 0.1-2.0 mg/kg.

Distribution

In XLH patients, the observed volume of distribution of burosumab approximates the volume of plasma, suggesting limited extravascular distribution.

Biotransformation

Burosumab is composed solely of amino acids and carbohydrates as a native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination

Due to its molecular size, burosumab is not expected to be directly excreted. The clearance of burosumab is dependent on body weight and estimated to be 0.290 L/day and 0.136 L/day in a typical adult (70 kg) and pediatric (30 kg) XLH patient, respectively, with corresponding disposition half-life ($t_{1/2}$) in the serum ranging from approximately 16 to 19 days. Given the $t_{1/2}$ estimates, the estimated time to reach the plateau of steady-state exposures is approximately 67 days. Following multiple dose administration to pediatric subjects, observed serum trough concentrations reach a plateau by 8 weeks after initiation of treatment.

Linearity/non-linearity

Burosumab displays time-invariant pharmacokinetics that is linear to dose over the subcutaneous dose range of 0.1 to 2.0 mg/kg.

Pharmacokinetic/pharmacodynamic relationship(s)

With the subcutaneous route of administration, a direct PK-PD relationship between serum burosumab concentrations and increases in serum phosphate concentration is observed and well described by an E_{max} /EC_{50} model. Serum burosumab and phosphate concentrations, as well as TmP/GFR, increased and decreased in parallel and reached maximum levels at approximately the same time point after each dose, supporting a direct PK-PD relationship. The AUC for the change from baseline in serum phosphate, TmP/GFR and $1,25(OH)_2D$ increased linearly with increasing burosumab AUC.

Pediatric PK/PD

No significant difference has been observed in pediatric patient pharmacokinetics or pharmacodynamics as compared with PK/PD in the adult population. Burosumab clearance and volume of distribution are body weight dependent.

Special Populations

Population PK analyzes using data from pediatric and adult subjects who have XLH indicated that age, sex, race, ethnicity, baseline serum albumin, baseline serum alkaline phosphate, baseline serum alanine aminotransferase, and baseline creatinine clearance ≥ 49.9 mL/min, were not significant predictors of burosumab PK.

Post-Prandial Effect on Serum Phosphate and Calcium

The effect of burosumab on serum phosphate and calcium levels after food was investigated in two sub-studies (Study UX023-CL301 and UX023-CL303); 13 pediatric patients (aged >3 years) and 26 adult patients (aged 24-65 years). Serum phosphate and calcium were measured at the end of the treatment interval in pediatric patients and mid-interval in adults. Blood samples were taken after a period of fasting, and again 1-2 hours after a standardized meal.

Burosumab treatment did not cause post-prandial excursions above the age-adjusted upper limits of normal in serum phosphate or serum calcium in any pediatric or adult subject in the sub-studies.

5.3. Preclinical safety data

Adverse reactions in non-clinical studies with normal animals were observed at exposures which resulted in serum phosphate concentration greater than normal limits. These effects were consistent with an exaggerated response to the inhibition of normal FGF23 levels resulting in a supraphysiologic increase in serum phosphate beyond the upper limit of normal.

Studies in rabbits and adult and juvenile cynomolgus monkeys demonstrated dose-dependent elevations of serum phosphate and $1,25(OH)_2D$ confirming the pharmacologic actions of burosumab in these species. Ectopic mineralization of multiple tissues and organs (e.g. kidney, heart, lung, and aorta), and associated secondary consequences (e.g. nephrocalcinosis) in some cases, due to hyperphosphataemia, was observed in normal animals at doses of burosumab that resulted in serum phosphate concentrations in animals greater than approximately 8 mg/dL (2.6 mmol/L). In a murine model of XLH, a significant reduction in the incidence of ectopic mineralization was observed at equivalent levels of serum phosphate, suggesting that the risk of mineralization is less in the presence of excess FGF23.

Bone effects seen in adult and juvenile monkeys included changes in bone metabolism markers, increases in thickness and density of cortical bone, increased density of total bone and thickening of long bone. These changes were a consequence of higher than normal serum phosphate levels, which accelerated bone turnover and also led to periosteal hyperostosis and a decrease in bone strength in adult animals, but not in juvenile animals at the doses tested. Burosumab did not promote abnormal bone development, as no changes in femur length or bone strength were noted in juvenile animals. Bone changes were consistent with the pharmacology of burosumab and the role of phosphate in bone mineralization, metabolism and turnover.

In repeat-dose toxicology studies of up to 40 weeks duration in cynomolgus monkeys, mineralization of the rete testis/seminiferous tubules was observed in male monkeys; however, no changes were observed in semen analysis. No adverse effects on female reproductive organs were observed in these studies.

In the reproductive and developmental toxicology study performed in pregnant cynomolgus monkeys, moderate mineralization of the placenta was seen in pregnant animals given 30 mg/kg of burosumab and occurred in animals with peak serum phosphate concentration greater than approximately 8 mg/dL (2.6 mmol/L). Shortening of the gestation period and associated increased incidence of premature births were observed in pregnant monkeys at doses of ≥ 0.3 mg/kg which corresponded to burosumab exposures that are ≥0.875- to 1.39-fold anticipated clinical levels. Burosumab was detected in serum from fetuses indicating that burosumab was transported across the placenta to the fetus. There was no evidence of teratogenic effects. Ectopic mineralization was not observed in fetuses or offspring and burosumab did not affect pre- and postnatal growth including survivability of the offspring.

In preclinical studies, ectopic mineralization has been observed in normal animals, most frequently in the kidney, given burosumab at doses that resulted in serum phosphate concentrations greater than 8 mg/dL (2.6 mmol/L). Neither new or clinically meaningful worsening of nephrocalcinosis nor ectopic mineralization have been observed in clinical trials of patients with XLH treated with burosumab to achieve normal serum phosphate levels.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

L-histidine
D-sorbitol (E 420)
Polysorbate 80 (E 433)
L-methionine
Hydrochloric acid, 10% (for pH adjustment)
Water for injections

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.
Store in the original package in order to protect from light.

6.5. Nature and contents of container

Clear glass vial with butyl rubber stopper, and aluminum seal.
Pack size of one vial

6.6. Special precautions for disposal and other handling

Each vial is for single use only.
Do not shake the vial before use.

Before administration, the solution should be inspected visually. The liquid should be clear to slightly opalescent, colourless to pale brown-yellow. If the solution is cloudy, discoloured or contains particles, the solution should not be used.

After removing the vial from the refrigerator, allow the vial to reach room temperature for 30 minutes before injecting burosumab.

Burosumab should be administered using aseptic technique and sterile disposable syringes and injection needles.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LOCAL MARKETING AUTHORIZATION HOLDER

DKSH MALAYSIA SDN. BHD.
B-11-01, THE ASCENT, PARADIGM
NO. 1, JALAN SS7/26A,
KELANA JAYA, 47301 PETALING JAYA, MALAYSIA

8. DATE OF REVISION OF THE TEXT

February 2026