Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Crysvita

Active ingredient: Burosumab

Sponsor: Kyowa Kirin Australia Pty Ltd

July 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
ADA	Anti-drug antibodies
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
BPI	Brief Pain Inventory
$C_{avg,ss}$	Average concentration at steady-state
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CL/F	Apparent clearance
DMP	Disease monitoring program
eGFR	Estimated glomerular filtration rate
FGF23	Fibroblast growth factor-23
FEP	Fractional excretion of phosphorus
GEE	Generalised estimating equation
GFR	Glomerular filtration rate
ISR	Injection site reaction
KRN23	Drug development code for burosumab
LLN	Lower limit of normal
LSM	Least square means
Nab	Neutralising antibody
P1NP	Procollagen type 1 N-propeptide
PASS	Post authorisation safety study (European Union)
PD	Pharmacodynamic(s)

Abbreviation	
PHEX	Phosphate regulating endopeptidase homolog X-linked
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetic
QTc	QT interval corrected
RLS	Restless legs syndrome
RMP	Risk management plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
T_{max}	Time of maximum concentration
TmP/GFR	Ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate
TRP	Tubular reabsorption of phosphate
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
XLH	X-linked hypophosphataemia

Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Crysvita
Active ingredient:	Burosumab
Decision:	Approved
Date of decision:	3 September 2021
Date of entry onto ARTG:	10 September 2021
ARTG numbers:	340793, 340796 and 340797
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Kyowa Kirin Australia Pty Ltd, 68 York Street, NSW 2000
Dose form:	Solution for injection
Strength:	10 mg/mL, 20 mg/mL and 30 mg/mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	*Crysvita (burosumab) is indicated for the treatment of X-linked hypophosphataemia (XLH) in adults, adolescents and children 1 year of age or older.*
Route of administration:	Subcutaneous injection
Dosage:	Treatment should be initiated and monitored by specialist medical practitioners experienced in the management of patients with metabolic bone disease. Dosage of Crysvita is based on multiple factors, including the age, the body weight and the serum phosphate concentration of the patient. For further information regarding dosage, refer to the Product Information.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Pregnancy category:	B3 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Kyowa Kirin Australia Pty Ltd (the sponsor) to register Crysvita (burosumab) 10 mg/mL, 20 mg/mL and 30 mg/mL, solution for injection for the following proposed indication:

> *The treatment of X-linked hypophosphataemia in paediatric patients 1 year of age and older and adults.*

X-linked hypophosphataemia (XLH) is a rare, serious, chronically debilitating condition associated with a mutation in the *PHEX* (phosphate regulating endopeptidase homolog X-linked) gene on the X-chromosome. The mutation impairs the phosphate sensing control system that impacts bone mineralisation and musculoskeletal function through excess production of fibroblast growth factor-23 (FGF23) and resultant hypophosphataemia. X-linked hypophosphataemia is characterised by excess levels of circulating FGF23 that leads to increased urinary phosphate excretion, reduced activated vitamin D (1,25-dihydroxyvitamin D, calcitriol. $1,25(OH)_2D$) synthesis, and subsequent hypophosphataemia resulting in defective bone mineralisation.

In children, the skeletal components of XLH manifest primarily as osteomalacia and rickets, a disease of the growth plates characterised by deficient mineralisation and delayed endochondral ossification, that lead to reduced growth and skeletal deformities including bowing of the lower extremities. The height growth deficiency caused by the growth plate defects can lead to a permanent loss of growth potential. Rickets and the accompanying skeletal deformities burden paediatric patients with daily pain, gait abnormalities, and impaired physical functioning, such that a young child may be severely limited in their daily activities.

As an adolescent with XLH enters puberty, and the growth plates close, the radiologic abnormalities that specifically define rickets are no longer apparent. However, hypophosphataemia, osteomalacia, short stature, and lower extremity deformities typically persist through adulthood. Many adolescents and young adults require orthopaedic surgery to correct residual lower limb defects following cessation of growth.

Adults with XLH experience significant morbidity due to years of chronic hypophosphataemia. Their bones may be particularly prone to pathologic fractures and pseudofractures due to a combination of the skeletal deformities from childhood that

expose the bone to significant stress resulting from uneven biomechanical loading, and osteomalacia, which is associated with impaired bone remodelling. Adults with XLH also commonly develop early osteoarthritis as a result of the continued weight bearing on lower limbs that have mechanical axis defects from childhood.

Conventional therapy for XLH consists of oral phosphate combined with active vitamin D. The goal of therapy is to supplement the body's pool of phosphate in order to allow mineralisation of bone and improve skeletal outcomes and associated symptoms. The sponsor comments that, the efficacy of conventional treatment in improving skeletal outcomes in children has not been demonstrated in prospective, randomised clinical trials. Retrospective reports suggest that growth remains suboptimal in many patients and orthopaedic intervention may be required to correct leg deformities.

In adults, oral phosphate/active vitamin D therapy may be initiated (or maintained) for the treatment of osteomalacia, bone/joint pain and other symptoms, and fractures or pseudofractures, but evidence of efficacy to improve osteomalacia, bone mineral density, microarchitecture or pain in adults is limited or the data shows absence of positive effect.

Following the closure of long bone growth plates and attainment of peak height in adolescents, the bone continues to grow periosteally and strengthen within the cortical and trabecular regions. Reaching the potential peak bone mass in the second or third decade of life carries protection against premature osteoporosis and fracture risk. However, the multiple daily doses of oral phosphate required for treatment produce a transient and intermittent increase in serum phosphorus that can exacerbate phosphate wasting because impairment of renal phosphate reabsorption is not addressed. This intermittent phosphate load triggers high urinary phosphate excretion and increases the risk and progression of nephrocalcinosis, which has been reported to occur in as many as 33% to 100% of patients with XLH in the early of years of more aggressive therapy. Given the high rate of complications, use of lower phosphate dosing strategies to improve safety were implemented. This reduced the associated safety issues but was also a less effective regimen and led to a lower but still substantial level of nephrocalcinosis of 25% to 30%. In some instances, the compensatory increases in parathyroid hormone following conventional therapy may increase the risk of secondary or tertiary hyperparathyroidism, especially if treatment is episodic, variable or associated with inappropriately balanced phosphate/vitamin D therapy. Moreover, frequent daily dosing, associated adverse effects and the need for regular monitoring of patients may compromise treatment persistence/compliance and therapeutic benefit of conventional therapy.

Burosumab is a recombinant fully human immunoglobulin G subclass 1 (IgG1) monoclonal antibody (mAb) that binds to and inhibits the excessive biological activity of FGF23, thereby treating the underlying cause of XLH.

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU) on 19 February 2018 (for children one year of age and older and adolescents with growing skeletons) and 30 September 2020 (children and adolescents aged one to 17 years with radiographic evidence of bone disease, and in adults); in the United States of America (USA) on 17 April 2018 (adult and paediatric patients one year of age and older) and 27 September 2019 (in adult and paediatric patients six months of age and older); Canada on 5 December 2018 (adult and paediatric patients one year of age and older) and 16 June 2020 (adult and paediatric patients six months of age and older); Brazil on 21 March 2019; Japan on 20 September 2019; and in Switzerland on

20 January 2020. A similar application was under consideration in Singapore, submitted on 24 September 2019.

Table 1 provides an overview of the indications approved overseas.

Table 1: International regulatory status of selected countries

Region	Submission date	Status	Approved indications
European Union (EU), via centralised procedure	30 November 2016	Approved 19 February 2018	*The treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons*
	27 August 2019	Approved 30 September 2020	*The treatment of XLH, in children and adolescents aged one to 17 years with radiographic evidence of bone disease, and in adults*
	17 December 2020	Under consideration	*The treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged one year and over*
USA	17 August 2017	Approved 17 April 2018	*The treatment of XLH in adult and paediatric patients one year of age and older*
	11 December 2018;[2] 29 March 2019;[3]	Approved 27 September 2019	*The treatment of XLH in adult and paediatric patients six months of age and older*
	18 December 2019	Approved18 June 2020	*The treatment of FGF23-related hypophosphatemia in TIO associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in adult and paediatric patients two years of age and older*

[2] Application to revise the US-PI for updating the results of adult Phase III study (Study UX023-CL303)
[3] Application to extend the indication for paediatric XLH patients aged 6 to 12 months and to revise the US-PI for including the result of paediatric Phase III study (Study UX023-CL301).

Region	Submission date	Status	Approved indications
Canada	11 May 2018	Approved 5 December 2018	*The treatment of XLH in adult and paediatric patients one year of age and older*
	28 June 2019	Approved16 June 2020	*The treatment of XLH in adult and paediatric patients six months of age and older*
	1 February 2021	Under consideration	*The treatment of FGF23-related hypophosphataemia in TIO associated with tumours that cannot be curatively resected or localised in adult and paediatric patients one year of age and older*
Japan	7 January 2019	Approved 20 September 2019	*FGF23-related hypophosphataemic rickets and osteomalacia*
Switzerland	31 August 2018	Approved20 January 2020	*The treatment of XLH in adults, adolescents and children one year of age and older*
Singapore	24 September 2019	Under consideration	*The treatment of XLH in adult and paediatric patients one year of age and older*

Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-03892-1-5

Description	Date
Priority Determination;[4] Orphan Designation;[5]	16 July 2020 16 July 2020
Submission dossier accepted and first round evaluation commenced	7 September 2020
Evaluation completed	19 February 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	9 March 2021
Sponsor's pre-Advisory Committee response	24 March 2021
Advisory Committee meeting	8 and 9 April 2021
Registration decision (Outcome)	3 September 2021
Completion of administrative activities and registration on the ARTG	10 September 2021
Number of working days from submission dossier acceptance to registration decision*	143

*Target timeframe for priority applications is 150 working days from acceptance for evaluation to the decision.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[4] The TGA has implemented a priority pathway for the registration of novel prescription medicines for Australian patients. The priority pathway provides a formal mechanism for faster assessment of vital and life-saving prescription medicines. The target timeframe of 150 working days is up to three months shorter than the standard prescription medicines registration process.

[5] 'Orphan drugs' are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

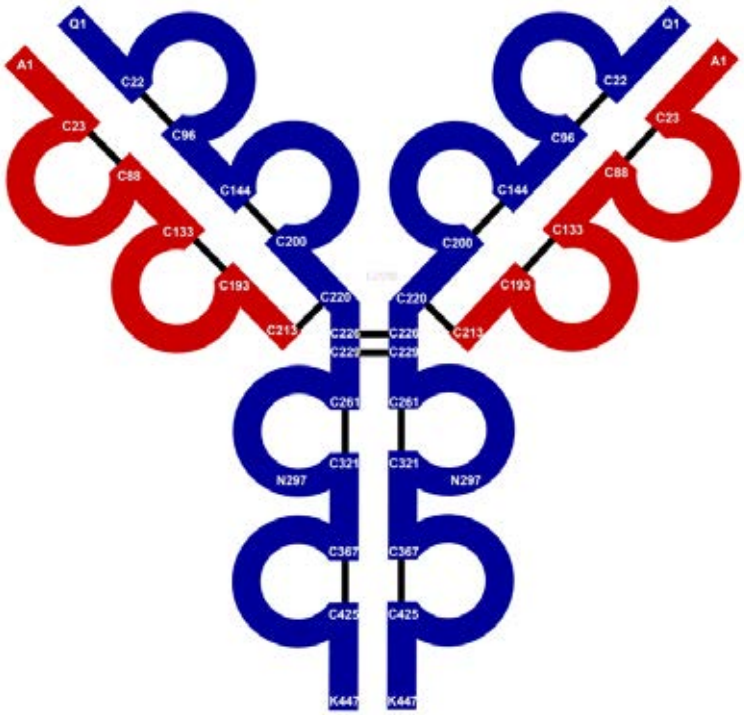
Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Burosumab is a human immunoglobulin G subclass 1 (IgG1) type antibody composed of two heavy chain (γ1-chain) molecules and two light chains (κ-chain) molecules (Figure 1).

Figure 1: Crysvita (burosumab) primary structure



Heavy chains are shown in blue and light chains are shown in red

Black lines show the location of disulfide bonds

N297 of heavy chain: glycosylation site

Burosumab has complementarity determining regions (CDRs) derived from mouse anti-human FGF23. It binds to excess FGF23 in biological fluid. Burosumab neutralises excess FGF23, inhibiting an interaction between soluble FGF23 and FGF23 receptor complex on the cell surface.

By inhibiting FGF23, burosumab restores tubular reabsorption of phosphate from the kidney and increase the production of 1,25-dihydroxy vitamin D (1,25(OH)2D), which enhances intestinal absorption of calcium and phosphate. Together, these actions improve serum phosphorus levels and bone mineralisation.

The data submitted support a shelf life of 36 months when stored at 2 to 8°C with protection from light. Temperature excursions were not requested.

Crysvita is available in a vial and is visually identified as clear to slightly opalescent, colourless to pale brownish-yellowish solution.

The data supplied in relation to the physical and chemical properties of burosumab were satisfactory. There are no issues pertaining to the specifications or the stability of the drug

substance or the drug product. All manufacturing steps and analytical procedures were validated.

There are no objections to the registration of this product from sterility, endotoxin, container safety or an adventitious agent perspective.

The quality evaluator has no objections to the registration of Crysvita on quality grounds. Overall, the supplied data was satisfactory and there are no further quality related concerns. Sufficient evidence was provided to demonstrate that the risks related to the manufacturing quality of Crysvita have been controlled to an acceptable level.

Nonclinical

The nonclinical evaluator raised no objections to the registration of Crysvita for the proposed indication. The submitted primary pharmacology studies were supportive of the use of burosumab in the proposed indication.

In vitro, burosumab was shown to bind to human FGF23, and recognise the rabbit and cynomolgus monkey forms of FGF23, resulting in inhibition of FGF23 induced signalling. *In vivo*, treatment with burosumab increased serum phosphate and 1,25 dihydroxyvitamin D levels and decreased urinary phosphate excretion in rabbits and monkeys, consistent with inhibition of the biological actions of FGF23. A study in a mouse model of XLH, performed using a surrogate antibody (able to recognise murine FGF23), showed prevention of growth retardation in juvenile animals and improved bone mineralisation.

No cross reactivity was seen with burosumab in experiments with human, monkey and rabbit tissues. Antibody dependent cell mediated cytotoxicity activity by burosumab was demonstrated *in vitro* but was not apparent (or not readily so) *in vivo*.

The safety pharmacology assessment revealed no effect of burosumab on the central nervous system or respiratory function and no direct effect on cardiovascular function. Changes in cardiovascular parameters (increased heart rate, ST depression and reduced stroke volume, ejection fractions and end diastolic volumes) were observed with extended treatment in monkeys. This was considered a consequence of ectopic mineralisation of the heart and aorta (secondary to drug induced hyperphosphataemia) rather a direct effect of burosumab on cardiac function.

The pharmacokinetic profile of burosumab was typical of an immunoglobulin G (IgG) antibody, and similar in the laboratory animal species and humans. This was characterised by slow subcutaneous (SC) absorption, limited distribution, and a long serum half-life. Bioavailability by the SC route was high to complete.

Burosumab showed a low order of acute toxicity in monkeys, and a moderate order of acute toxicity in rabbits. Mortality following single dose administration was only observed in rabbits and was related to renal failure following mineralisation of the kidney (occurring secondary to the pharmacologically mediated increase in serum phosphate levels).

Repeat dose toxicity studies were conducted with burosumab in rabbits (14 weeks) and adult and juvenile cynomolgus monkeys (up to 40 weeks duration). Doses were given once every two weeks, and mainly by the intravenous (IV) route, although SC administration was included in the pivotal monkey study. Ectopic mineralisation, affecting the kidney, lung, heart, aorta and various other tissues, was the major treatment related finding. Occurring as a consequence of exaggerated pharmacology, this is of limited clinical relevance. Hyperphosphataemia also drove accelerated and inappropriate bone turnover, but positive effects on bone were seen as well (increases in bone mineral density and content).

No genotoxicity or carcinogenicity studies were conducted with burosumab, which was considered acceptable. No particular cause for concern for carcinogenicity is seen from the general repeat dose toxicity program or from knowledge of the physiological role of the target.

No effects on male and female fertility are predicted based on semen analysis and examination of reproductive tissues in monkeys (in lieu of functional studies). Burosumab was found to increase fetal loss and pre-term births and shorten gestation duration in pregnant monkeys. These effects were observed at a large multiple of the clinical exposure at the maximum recommended dose in adults (64-fold), were relatively modest in size, and occurred in conjunction with placental mineralisation, suggesting limited clinical relevance. Placental transfer of burosumab was evident in the monkey. Ectopic mineralisation of fetal tissues was not observed, nor malformations or effects on growth, development of survival of the offspring. The nonclinical evaluator supports assignment to pregnancy category B3.[6]

Clinical

The clinical dossier consisted of the following studies:

- Two Phase I studies
- Two Phase II studies
- Six Phase III studies
- Three Phase I/II studies

Pharmacology

Pharmacokinetics

The observed pharmacokinetics (PK) data in adult patients with X-linked hypophosphataemia (XLH) aged ≥ 18 years were based on intensive sampling allowing for non-compartmental analysis and from population pharmacokinetics (popPK) modelling. The observed PK data for children aged one to 12 years with XLH were based on sparse sampling, with the data being pooled with data from adults for PK modelling. There were no observed PK data in adolescents aged > 12 years to ≤ 17 years, and PK in these patients were based on popPK modelling of the pooled data from children and adults.

Burosumab exhibited linear pharmacokinetics following subcutaneous injections within the dose range of 0.1 to 1 mg/kg (0.08 to 0.8 times the maximum approved recommended dosage based on a 70 kg patient). The steady state trough mean (± standard deviation (SD) concentration of burosumab was 5.8 (± 3.4) µg/mL in adult patients aged 18 to 65 years, 15.8 (± 9.4) µg/mL in patients aged five to 12 years, and 14.2 (± 4) µg/mL in patients aged one to four years.

The absorption of burosumab is slow following SC administration. Burosumab mean time of maximum concentration (T_{max}) values ranged from eight to 11 days. Median T_{max} is approximately seven to 13 days. The formulation used in the clinical studies is identical to the formulation proposed for marketing in Australia.

[6] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The apparent volume of distribution of burosumab is 7.35 L. There were no data on protein binding or erythrocyte distribution in humans. This is acceptable for a monoclonal antibody.

No studies have been performed to characterise burosumab elimination. Burosumab is a human monoclonal IgG1 antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

The clearance of burosumab is dependent on body weight and estimated to be 0.278 L/day in a typical adult (70 kg) XLH patient with corresponding disposition half-life ($t_{1/2}$) in the serum of approximately 18 days. There were no data on renal clearance. However, burosumab is not expected to be renally cleared. Steady state would be expected to be reached within 12 weeks if no dosing adjustments were required.

There were no dedicated PK studies in subjects with hepatic impairment. However, population PK modelling indicated that the covariates of alanine transaminase (ALT) and alkaline phosphate (ALP) had no impact on the PK of burosumab. Therefore, hepatic impairment is unlikely to have an impact on the PK of burosumab.

There were no dedicated PK studies in subjects with renal impairment. However, population PK modelling indicated that the covariates of creatinine or estimated creatinine clearance (CrCL) had no impact on the PK of burosumab. Therefore, renal impairment is unlikely to have an impact on the PK of burosumab.

There were no dedicated PK studies in subjects with different types of *PHEX* mutation. However, population PK modelling indicated that the covariate of *PHEX* mutation type had no impact on the PK of burosumab.

There were no studies assessing pharmacokinetic interactions between burosumab and other medicines. As burosumab is expected to be degraded via catabolic pathways, direct drug interactions with small molecule drugs that are metabolised by cytochrome P450 enzymes are unlikely.

Population pharmacokinetic data

The submission included a population pharmacokinetic (popPK) and pharmacokinetics/pharmacodynamics (PK/PD) report (Study ULTR-PMX-Burosumab-1280), which was based on data collected from nine clinical studies in adults and children with XLH (Study KRN23-US-02, Study KRN23-INT-001, Study KRN23-INT-002, Study UX203-CL201, Study UX203-CL203, Study UX203-CL205, Study UX203-CL303, Study UX023-CL301 and Study UX023-304). The pooled data were from six infants aged from one to two years, 88 children aged from two to 12 years and 183 adults aged > 17 years. The data comprised 3185 measurable serum burosumab concentrations and 6590 measurable serum phosphorus concentrations for PK and PK/PD analysis.

The median age of adult subjects was 41 years (range: 18.5 to 68 years), with a median body weight of 69 kg (range: 36.1 to 140). Median baseline weights were 10.4 kg in infants, 23.4 kg in children and 69 kg in adults. The majority of the subjects were White (83.3%, infants, 88.6%, children and 82.5%, adults). The majority of subjects in the total population had a pathogenic *PHEX* mutation. Marked differences were observed between paediatric (infants and children) and adult populations as regards the levels of bone and serum ALP as well as serum intact FGF 23. High inter-subject variability was observed for intact FGF23, and bone-specific ALP in adults.

The final unified population PK model for subjects with XLH reported in the report ULTR-PMX-Burosumab-1280 was a one-compartment model with weight based allometric functions on apparent clearance (CL/F) and the volume of the distribution (V/F), along with a first order rate of absorption from SC injection site.

The typical half-life of burosumab absorption from SC injection sites was estimated to be 1.8 days, suggesting near complete absorption within approximately nine days. Body weight has an allometric effect on burosumab clearance and volume of distribution, with estimated scaling exponents of 0.876 and 0.913, respectively. The typical values (standardised on body weight of 70 kg) of apparent clearance in serum (CL/F) and volume of distribution (V/F) were 0.278 L/day (relative standard error (RSE) = 2.5%) and 7.35 L (RSE = 3%), respectively. The CL/F suggests that burosumab is slowly eliminated following SC administration and the V/F suggests that burosumab is confined predominantly to the intravascular compartment with limited tissue distribution. These findings for CL/F and V/F are consistent with most other human monoclonal antibody drugs.

Posterior Bayes estimated geometric mean (CV%) elimination half life values derived with the final population PK model were 18.5 days (28.3%) in infants, 17.4 days (22.2%) in children and 18.1 days (32.1%) in adults. Posterior Bayes estimated geometric mean (coefficient of variation; CV%) accumulation ratios derived with the final population PK model were 2.92 (21.6%) in infants, 2.77 (17.1%) in children, and 1.64 (17.8%) in adults. The higher accumulation ratios in the paediatric population is explained by the shorter dosing interval of every two weeks in comparison to every four weeks in adult population.

Population PK analyses indicated that age, sex, race, ethnicity, baseline serum albumin, baseline serum ALP, baseline serum AST, and baseline creatinine clearance ≥ 49.9 mL/min, were not significant predictors of burosumab PK.

Pharmacodynamics

Pharmacodynamic (PD) assessments focused on serum phosphorous level as the primary PD endpoint, but also included evaluation of 1,25-dihydroxy vitamin D concentration and renal tubular reabsorption of phosphate as assessed by the tubular phosphate/glomerular filtration rate (TmP/GFR) ratio. The pharmacodynamic endpoints in the multiple dose studies submitted to support the efficacy and safety of burosumab for the treatment of XLH in adult and paediatric patients are discussed in the efficacy section as some PD endpoints were defined primary and/or secondary efficacy endpoints.

Following SC administration of burosumab to XLH patients, serum phosphate levels increased in a burosumab concentration-dependent manner. Higher burosumab concentrations were associated with greater increases in serum phosphate levels. The increase in serum phosphate was reversible and returned to near baseline levels when administration of burosumab was discontinued.

Renal tubular reabsorption of phosphorous, as assessed by the ratio of renal tubular maximum phosphate reabsorption rate to glomerular filtration rate (TmP/GFR), also showed burosumab dose-dependent increases from Baseline. Serum 1,25-dihydroxy vitamin D levels also increased with burosumab, but the increase was not accompanied by increased serum calcium and intact parathyroid hormone levels, or with changes in urinary calcium excretion. Both total and unbound serum FGF23 concentrations increased from Baseline values after burosumab administration in a dose dependent manner.

The population PK/PD model of subjects with XLH examined the relationship between serum burosumab concentrations (PK) and changes in serum phosphorus level (PD). The PK/PD data were adequately described by an E_{max} model;[7] from which the typical concentration at which effect is at half the maximum was estimated regardless of the subject's age, body weight or time on burosumab treatment. The best fitting model produced a constant half maximal effective concentration (EC_{50}) that is time invariant, suggesting that tolerability does not develop following repeat dosing of burosumab. Simulations of burosumab and phosphorous exposure using the PK/PD model reported

[7] The E_{max} model is a nonlinear model frequently used in dose-response analyses.

that for adolescent patients (13 to 17 years) who have XLH, the proposed dose regimen of 0.8 to 1.2 mg/kg once every two week is appropriate.

The relationships between burosumab exposures (C_{max}, C_{min} and area under the concentration versus time curve) and hyperphosphataemia in adults were examined. In this analysis, hyperphosphataemia was defined as an observation of serum phosphorus > 4.5 mg/dL from one or more laboratory measurements. Burosumab serum exposures were compared between 12 subjects, who had at least one hyperphosphataemic event versus those from adult XLH subjects who did not have hyperphosphataemia. PK exposure distributions demonstrated overlap between the two groups with similar median values. Therefore, it was concluded that the occurrence of hyperphosphataemia did not have any apparent association with burosumab serum exposures.

The incidence of anti-drug antibody (ADA) positivity was less than 10% in subjects who were negative at Baseline and had at least one ADA positive sample post-dose and subjects who had a positive sample at Baseline and had a boosted ADA response. Of the 94 paediatric subjects who were treated with burosumab with relevant immunogenicity data, 8 (8.5%) subjects were ADA positive and three (3.2%) of these subjects were neutralising antibody (NAb) positive. Of the 148 adult subjects with relevant immunogenicity data, 8 (5.4%) subjects were ADA positive, and no subjects were NAb positive. The presence of burosumab ADAs had no negative effects on PK (CL/F; V/F), serum phosphate concentration (PD), efficacy, or safety.

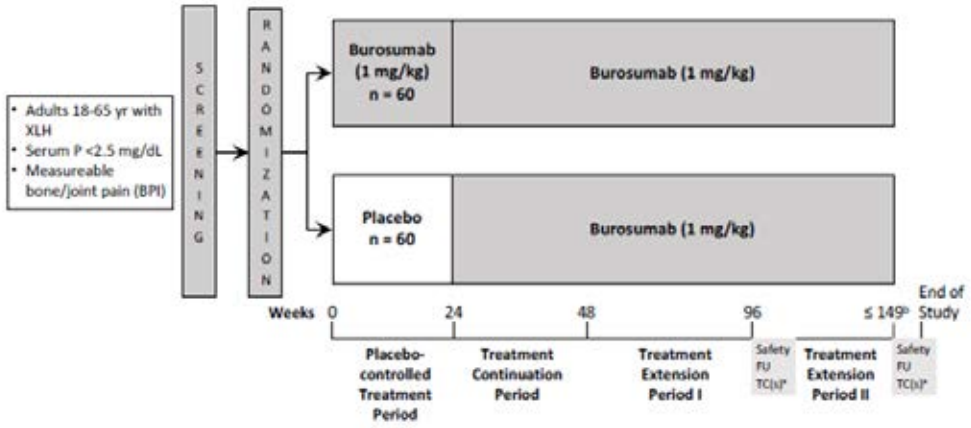
Efficacy in adults

Study UXCL23-CL303 (pivotal)

Study UXCL23-CL303 was a randomised, double-blind, placebo-controlled, multinational, multicentre, Phase III study designed to evaluate the efficacy and safety of burosumab in adult subjects with XLH. The primary objective was to establish the effect of burosumab treatment compared with placebo on increasing serum phosphorus levels. The key secondary efficacy objectives were to establish the effect of burosumab treatment compared with placebo on skeletal pain, stiffness, and physical functioning.

The study consisted of a placebo controlled treatment period (24 weeks), a burosumab open label treatment continuation period (24 weeks) followed by treatment continuation period I (48 weeks) and for the USA- and EU-located sites only, a second treatment extension period (maximum 53 weeks) (Figure 2).

Figure 2: Study UX023-CL303 Overview of study design



BPI = Brief Pain Inventory; FU = follow-up; serum P = serum phosphorus; XLH = X-linked hypophosphataemia

The study included adults aged 18 to 65 years, with a diagnosis of XLH plus clinical features of adult XLH. Subjects had a documented *PHEX* mutation in either the patient or in a directly related family member with appropriate X-linked inheritance and/or serum intact FGF 23 level > 30 pg/mL. Patients were required to have biochemical findings consistent with XLH (fasting serum phosphorus and TmP/GFR both < 2.5 mg/dL) and skeletal pain attributed to XLH/osteomalacia. Estimated glomerular filtration rate (eGFR) had to be ≥ 60 mL/min or 45 to < 60 mL/min with confirmation that any renal insufficiency was not due to nephrocalcinosis.

Patients were excluded if they were on active treatment for XLH. Medications with exclusion periods were pharmacologic vitamin D metabolite or analogue or oral phosphate, aluminium hydroxide antacids, acetazolamides, thiazides, chronic systemic corticosteroids, medications to suppress parathyroid hormone, bisphosphonates, denosumab, or teriparatide. Patients were also excluded if their corrected serum calcium level was ≥ 10.8 mg/dL at screening Visit two and/or their serum intact parathyroid hormone was ≥ 2.5 x upper limit of normal at screening Visit one.

During the 24 week placebo controlled treatment period, subjects received either burosumab 1 mg/kg SC once every four weeks or matching placebo. During the treatment continuation and extension periods, all subjects received open label burosumab at the same dose.

A total of 163 subjects were screened and 134 subjects were enrolled and randomised in a 1:1 ratio to receive burosumab (68 subjects) or placebo (66 subjects) for 24 weeks during the placebo controlled treatment period. Randomisation was stratified by pain intensity and region.

The mean standard deviationage at Baseline was 40 (12.2) years (range: 18.5 to 65.5 years). The majority of subjects were female (65%) and White (80.6%). Mean (SD) time since first XLH symptoms and XLH diagnosis was 37.2 (12.77) years and 31.4 (15.6) years, respectively. 98.5% of subjects in the placebo group and 92.6% of subjects in the burosumab group had *PHEX* mutations. Most subjects in both treatment groups had received prior therapy with both oral phosphate and active vitamin D metabolites or analogues. Key PD parameters at baseline were comparable between the two treatment groups.

The majority of subjects had a baseline Brief Pain Inventory (BPI) worst pain score of > 6 and pain medication use was similar between treatment groups at Baseline. Most subjects had bowing of limbs (94%) and enthesopathy (99.3%). Nearly two thirds of subjects had osteoarthritis (63.4%). Active fractures and active pseudofractures were identified in 11.9% and 47% of subjects respectively. Non-active fractures and non-active pseudo fractures were identified in 59% and 34.3% of subjects respectively.

The primary endpoint was the proportion of subjects achieving mean serum phosphorus levels above the lower limit of normal (LLN) at the midpoint of the dose interval, as averaged across dose cycles between baseline and Week 24. The primary endpoint was met by 92.6% of subjects in the burosumab group, compared to only 7.6% of subjects in the placebo group ($p < 0.0001$) (Table 3). The results of the sensitivity and subgroup analyses were consistent with the primary analysis.

Table 3: Study UX023-CL303 Proportion of subjects achieving mean serum phosphorous levels above the lower limit of normal across midpoints of dose intervals through Week 24, primary analysis set.

Parameter Statistics	Placebo (N = 66)	Burosumab (N = 68)
Achieved Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24 - n (%)	5 (7.6)	63 (92.6)
95% CI[a]	(3.3, 16.5)	(83.9, 96.8)
p-value[b]		< 0.0001

CI = confidence interval; LLN = lower limit of normal (2.5 mg/dL)

[a] The 95% CI for the proportion of subjects who achieve mean serum phosphorus levels above the LLN are calculated using the Wilson score method.

[b] The p-value is from Cochran-Mantel-Haenszel testing for association between achieving mean serum phosphorus levels above the LLN and treatment group, adjusting for the actual randomisation stratification of Brief Pain Inventory Average Pain and region.

The key secondary endpoints were changes from Baseline to Week 24 in BPI worst pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Physical functioning, and WOMAC stiffness scores between the two treatment groups. Statistical significance was only achieved for the WOMAC stiffness endpoint. The least square (LS) mean reductions from Baseline at Week 24 for the other two other key secondary efficacy endpoints of pain and physical function numerically favoured the burosumab group, but neither of the comparisons were statistically significant (Table 4).

For subjects originally assigned to burosumab and continuing on open label treatment, further improvements in BPI worst pain, WOMAC stiffness, and WOMAC physical function scores were observed in the treatment continuation period. For subjects originally assigned to placebo and switching to burosumab, improvement in BPI worst pain, WOMAC stiffness, and WOMAC physical function scores were observed in the treatment continuation period.

The study included an exploratory efficacy endpoint assessing healing of active pseudofractures and/or fractures. A baseline skeletal survey was conducted to identify the number of pre-existing fractures/pseudofractures. At Week 24, 43.1% (28 out of 65 fractures) of active fractures/partial fractures in the burosumab group had fully healed compared to 7.7% (7 out of 91 fractures) in the placebo group. At Week 48, 63.1% (41 out of 65 fractures) of active fractures/partial fractures in the burosumab group had fully healed compared to 35.2% (32 out 91 fractures) in the placebo that were switched over to burosumab group.[8]

There was also an additional secondary efficacy endpoint for the PD parameter ratio of renal TmP/GFR. The TmP/GFR improved with burosumab treatment, consistent with the observed improvements in serum phosphorus. In contrast, the TmP/GFR remained relatively unchanged in the placebo group until the transition to burosumab treatment at Week 24. At Baseline, the mean (SD) TmP/GFR was 1.68 (0.4) mg/dL (range: 1 to 3.4) in the burosumab group. At Week 24, the mean (SD) TmP/GFR was 2.21 (0.483) mg/dL in the burosumab group. The LS means standard error increase in TmP/GFR from Baseline to Week 24 in the burosumab group was 0.56 (0.11) mg/dL, representing an LS mean (standard error) percentage increase of 35.8% (6.13%). Increases in TmP/GFR due to burosumab were accompanied by small increases in tubular reabsorption of phosphate (TRP). The mean (SD) TRP at Baseline was 0.81 (0.083) for the burosumab group and increased to 0.84 (0.065) at Week 24. There were no clinically meaningful changes in two hour or 24 hour phosphorus excretion in any of the treatment groups during the study.

[8] At Week 24, the participants that were in placebo group were switched over to burosuman (1 mg/kg).

Table 4: Study UX023-CL303 Key secondary endpoints at Week 24

Key Secondary Endpoint Statistics	Placebo (N = 66)	Burosumab (N = 68)
Worst Pain, by BPI		
Baseline, n	66	68
Mean (SD)	6.54 (1.433)	6.81 (1.308)
Week 24, n	65	67
Mean (SD)	6.09 (2.013)	5.82 (1.916)
Mean (SE) Change from Baseline	-0.42 (0.218)	-0.98 (0.191)
LS Mean (SE) Change from Baseline	-0.32 (0.222)	-0.79 (0.211)
LS Mean (SE) Difference (Burosumab-Placebo)	**-0.46 (0.275)**	
p-value	**0.0919**	
Significance Level for Test	0.05	
Significant?	**No**	
Physical Functioning, by WOMAC		
Baseline, n	66	68
Mean (SD)	43.89 (19.938)	50.79 (19.660)
Week 24, n	65	66
Mean (SD)	42.65 (22.760)	43.43 (19.507)
Mean (SE) Change from Baseline	-0.97 (1.826)	-6.90 (1.886)
LS Mean (SE) Change from Baseline	+1.79 (2.722)	-3.11 (2.553)
LS Mean (SE) Difference (Burosumab-Placebo)	**-4.90 (2.479)**	
p-value	**0.0478**	
Significance Level for Test	0.025	
Significant?	**No**	
Stiffness, by WOMAC		
Baseline, n	66	68
Mean (SD)	61.36 (20.770)	64.71 (20.253)
Week 24, n	65	67
Mean (SD)	60.38 (21.827)	53.73 (20.759)
Mean (SE) Change from Baseline	-0.77 (2.698)	-10.63 (2.987)
LS Mean (SE) Change from Baseline	+0.46 (3.139)	-7.85 (3.034)
LS Mean (SE) Difference (Burosumab-Placebo)	**-8.31 (3.251)[a]**	
p-value	**0.0106[a]**	
Significance Level for Test	0.0167	
Significant?	**Yes**	

BPI = Brief Pain Inventory; LS = least squares; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Study UX023-CL304 (supportive)

Study UX023-CL304 was a multinational, multicentre, open label, single arm, Phase III study to evaluate the effects of burosumab on osteomalacia in adults with XLH. The primary objective was to establish the effect of burosumab treatment on improvement in XLH-associated osteomalacia as determined by osteoid volume/bone volume (OV/BV). The key secondary efficacy objectives were to establish the effect of burosumab treatment on increasing serum phosphorus levels. The main difference between study populations in Study UX023-CL304 and Study UX023-CL303 was that Study UX023-CL304 excluded subjects who had used oral phosphate/active vitamin D within the two years prior in order to avoid the confounding effects of conventional therapy on bone tissue.

Subjects were treated with open label burosumab 1 mg/kg once every four weeks. The study comprised three treatment periods: an open label treatment period (48 weeks), followed by an initial treatment extension period (I) (48 weeks) and an additional treatment extension period (II) for USA sites only (45 weeks).

The study enrolled male and female adult subjects ≥ 18 years of age with a diagnosis of XLH. Key inclusion criteria were similar to those outline for Study UX023-CL303. Key exclusion criteria included treatment with oral phosphate, vitamin D therapy or bisphosphonates within the two years prior to screening as well as evidence of hyperparathyroidism or the use of medication to suppress hyperparathyroidism within 60 days before screening.

A total of 25 subjects were screened and 14 were enrolled. 13 subjects completed the 48 weeks treatment period, of these subjects, five completed treatment extension period I. The remaining eight subjects from USA sites, completed treatment extension period II.

The mean age of subjects was 40 years (range: 25 to 52 years). The majority of subjects were female (57%) and White (64%). The mean (SD) time since XLH diagnosis was 32 (15.1) years. Most subjects had received therapy with both oral phosphate and active vitamin D metabolites or analogues two years prior to screening. The majority of subjects had not received conventional therapy as adults (64%).

The primary efficacy endpoint was the percent change from Baseline at Week 48 in osteoid volume/bone volume (OV/BV). For subjects with paired OV/BV data at Baseline and Week 48, there was a mean reduction of 54.2% (95% confidence interval (CI): 39.72, 68.64; nominal p< 0.0001).

The key secondary endpoint was the proportion of subjects achieving mean serum phosphorus levels above the LLN at the mid-point of the dose interval as averaged across dose cycles between baseline and Week 24. 13 subjects (93% (95% CI: 68.5%, 98.7%); nominal p < 0.0001) achieved the key secondary endpoint (Table 5).

Burosumab treatment also had a positive effect on change from Baseline at Week 48 in the additional osteomalacia-defining histomorphometric secondary efficacy endpoints of osteoid thickness, osteoid surface/bone volume, and mineralisation lag time.

Table 5: Study UX023-CL304 Summary of primary and secondary histomorphometric endpoints

	Osteoid Volume/ Bone Volume (OV/BV) (%)		Osteoid Thickness (O.Th) (µm)		Osteoid Surface/ Bone Surface (OS/BS) (%)		Mineralization Lag Time[a] (Mlt) (days)	
Statistic	Baseline	Week 48	Baseline	Week 48	Baseline	Week 48	Baseline	Week 48
n	10	11	11	11	11	11	11	10
Mean (SD)	26.1 (12.4)	11.9 (6.6)	17.2 (4.1)	11.6 (3.1)	91.7 (3.4)	67.8 (13.7)	1539.8 (1587.1)	195.5 (77.71)
Median	24.1	9.2	16.2	11.4	92.0	73.0	1378.4	233.4
Min, Max	8.8, 49.9	3.2, 25.6	12.1, 24.7	7.2, 18.6	85.0, 97.0	34.0, 81.0	129.6, 4909.1	69.8, 281.9
% Change from Baseline	-54.2% (mean)		-32.2% (mean)		-26.0% (mean)		-82.8% (median)	

Min = minimum; max = maximum; SD = standard deviation.

The percent change from Baseline is based on baseline of the subjects who had non-missing results at both baseline and Week 48 visits.

a Using imputed results if reported results are missing

Other secondary and exploratory efficacy results are discussed in the clinical evaluation report.

Study X023-CL203 (supportive)

Study X023-CL203 was an open label, long term extension study to evaluate the safety and PD of burosumab in adults subjects with XLH. The primary objectives related to the long term safety, PD and immunogenicity of burosumab. The study included exploratory efficacy objectives relating to patient reported outcomes and changes in bone disease as assessed by radiography.

Subjects who had participated in the completed Study KRN23-INT-001 or were eligible for study inclusion. The eGFR requirements were the same as those outlined for other studies

above. Key exclusion criteria were a safety related event in the preceding studies or the presence of nephrocalcinosis on renal ultrasound.

Subjects received starting does of burosumab of 0.3, 0.6 or 1 mg/kg every four weeks that matched their last dose in the preceding studies. Doses were titrated according to serum phosphorus levels.

A total of 20 subjects were enrolled, and 19 (95%) subjects completed the study. The mean (SD) age was 49.8 (12.9) years. Most subjects were female (70%) and White (95%). The mean (SD) time since XLH diagnosis was 40.7 (16.2) years and mean (SD) time since first XLH symptoms was 47.9 (13.5) years. All 20 enrolled subjects received burosumab through Week 68.

Efficacy endpoints were exploratory only. There were primary PD endpoints relating to serum phosphorus, 1,25(OH)2D, intact parathyroid hormone, and FGF23, urinalysis parameters (TmP/GFR, TRP, calcium, creatinine, phosphorus), bone biomarkers (total ALP, bone specific alkaline phosphatase carboxy terminal cross-linked telopeptide of type I collagen and procollagen type N- propeptide and fractional excretion of phosphorus (FEP).

At midpoint visits throughout the study most subjects (85% (17 out of 20) to 100% (20 out of 20) had serum phosphorus levels in the normal range. The mean (SE) serum phosphorus concentration at the midpoints of burosumab dosing was 3.10 (0.079) mg/dL, with a mean increase from Baseline of + 1.21 mg/dL. Mean serum phosphorus concentrations were consistently above baseline throughout the study.

Mean serum 1,25(OH)2D concentrations increased from Baseline to Weeks 12 and 24 with burosumab treatment, then returned to baseline levels at Week 36 and remained near baseline levels through the rest of the study.

Mean urinary two hour TmP/GFR improved from Baseline at all visits with burosumab treatment. The mean (SE) TmP/GFR was 1.583 (0.0574) mg/dL at Baseline (n = 20) and 2.039 (0.0769) mg/dL at EOS (n = 19), with the increase from Baseline to end of study being 0.48 (0.076) mg/dL.

No clinically meaningful changes from Baseline in mean urinary two hour tubular reabsorption fraction (TRP) or FEP occurred over the course of the study. At Baseline, the mean urinary two hour TRP was 0.78 (range: 0.66 to 0.96), and the LS mean change from Baseline ranged from - 0.01 to + 0.05. At Baseline, the mean urinary two hour FEP was 0.22 (range: 0.04 to 0.34), and the LS mean change from Baseline ranged from - 0.05 to + 0.01.

The C-terminal telopeptide levels increased from Baseline only at Week 24, while procollagen type N-propeptide levels increased from Baseline at Weeks 24 through 96. The ALP and bone specific alkaline phosphatase levels decreased from Baseline at Week 72 through Week 168 and extension of time.

Efficacy in children

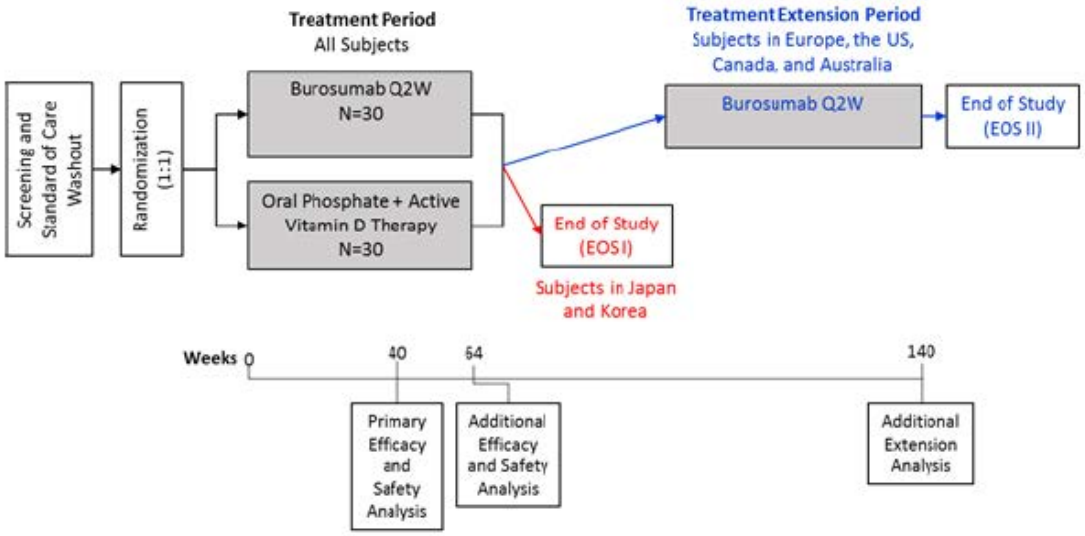
Study UX023-CL301 (pivotal)

Study UX023-CL301 was a randomised, open label, Phase III study to assess the efficacy and safety of burosumab versus oral phosphate and active vitamin D treatment in paediatric patients with XLH aged one to ≤ 12 years old. The primary objective was to evaluate the effect of burosumab therapy in improving rickets in children with XLH compared to active control. The secondary objectives were to evaluate the effects of burosumab compared to active control on: growth velocity and lower extremity deformity, PD markers that reflect phosphate homeostasis, biochemical markers of bone turnover

that reflect rickets severity and walking ability and patient/parent reported pain, fatigue and physical function/mobility outcomes.

The study consisted of treatment period (64 weeks), followed by a treatment extension period in which all subjects received burosumab. Only subjects from Europe, the USA, Canada and Australia were eligible to enter the treatment extension period (Figure 3). The study was open label but the radiologists who assessed radiographs for efficacy parameters were blinded to treatment group and baseline information.

Figure 3: Study UX023-CL301 Designed to study to assess the efficacy and safety of burosumab versus oral phosphate and active vitamin D treatment in paediatric patients with X-linked hypophosphataemia aged one to under 12 years old



EOS = end of study; Q2W = every 2 weeks

The study included male and female subjects ages one to ≤ 12 years of age with radiographic evidence of rickets with a Rickets Severity Score (RSS) total score of ≥ 2 and *PHEX* mutation or variant of uncertain significance in either the subject or in a directly related family member with appropriate X-linked inheritance. Subjects were required to have a serum phosphorus concentration < 3 mg/dL (< 0.97 mmol/L) and serum 25(OH)D concentration above the lower limit of normal (≥ 16 mg/mL) at the screening visit. Subjects also were required to have open epiphyses and to have received oral phosphate/active vitamin D therapy prior to the study. Key exclusion criteria included: evidence of hyperparathyroidism; hypocalcaemia or hypercalcaemia; height percentile > 50th; Tanner Stage 4 or higher; Grade 4 nephrocalcinosis; and planned orthopaedic surgery. Subjects were excluded if they had received or were currently receiving drugs known to delay puberty. Potential subjects receiving therapies that affected phosphorus metabolism or growth were eligible to enrol only after appropriate wash-out periods.

Eligible subjects discontinued oral phosphate and active vitamin D therapy seven days prior to randomisation. Subjects were randomised 1:1 to receive either open label burosumab SC once every two weeks or oral phosphate/active vitamin D therapy daily for a total of 64 weeks. Randomisation was stratified by baseline rickets severity, age and region. The starting dose of burosumab was 0.8 mg/kg, which could be increased to 1.2 mg/kg. The maximum allowable dose of burosumab per administration was 90 mg. Active control treatment was individualised for each subject at the investigator's discretion.

A total of 122 subjects were screened and 61 were randomised 1:1 to burosumab (29 subjects) or active control (32 subjects). All 61 subjects completed 64 weeks of treatment and were included in the efficacy and safety analysis. 51 subjects entered the

extension treatment period (26 from the active control group and 25 from the burosumab group).

The mean (SD) subject age was 6.3 (3.31) years (range 1 to 12.9 years). 44.3% of subjects were male and 55.7% were female. The key baseline demographics factors were reasonably well balanced between the two treatment groups. The XLH medical history of the two treatment groups were generally comparable, although there were numerical differences of note (≥ 10% difference between the two groups) for some conditions (that is, in-toeing, joint stiffness, craniosynostosis). Most subjects (55 out of 61 (90%)) were positive for pathogenic mutations in the *PHEX* gene. Ricketts Severity Score at Baseline was similar in the two treatment groups. The majority of subjects in both treatment groups had radiographic abnormalities at all examined sites.

The primary efficacy endpoint was the change in RSS at Week 40 as assessed by the disease specific radiographic global impression of change (RGI-C) global score. Burosumab was associated with statistically significantly greater healing compared to the active control group at Week 40 (least squares means (LSM) difference = 1.14 (95% CI: 0.83, 1.45), p < 0.0001), and continued improvement was seen at Week 64 in the burosumab compared to the active control group (LSM difference = 1.02 (95% : 0.72, 1.33), p < 0.0001) (Table 6). The efficacy results for the subgroup analyses based on the Radiographic Global Impression of Change (RGI-C) global scores were consistent with efficacy results for the analysis in the overall study population.

Table 6: Study UX023-CL301 Improvement in rickets as assessed by the Radiographic Global Impression of Change global score, primary assessment at Week 40, analysis of covariance and generalised estimating equation models.

RGI-C Score[a]	Active Control (N = 32)	Burosumab (N = 29)
RGI-C Global Score (primary endpoint at Week 40)		
Week 40[b] – LS mean (SE)	+0.77 (0.107)	+1.92 (0.110)
Difference (burosumab – active control) (95% CI)	1.14 (0.83, 1.45)	
p value	< 0.0001	
Week 64[c] – LS mean (SE)	+1.03 (0.136)	+2.06 (0.072)
Difference (burosumab – active control) (95% CI)	1.02 (0.72, 1.33)	
p value	< 0.0001	
	Active Control→ Burosumab	**Burosumab→ Burosumab**
Week 88 – n	15	6
Mean (SD)	+1.89 (0.349)	+2.11 (0.272)
LS mean difference (Week 88 – 64) (95% CI)	+0.91 (0.65, 1.17)	-
p value	< 0.0001	-

ANCOVA = analysis of covariance, CI = confidence interval, GEE = generalised estimation equation, LS = least squares, RGI-C = Radiographic Global Impression of Change, SE = standard error, SD = standard deviation.

a. The RGI-C score was based on a 7-point ordinal scale ranging from - 3 (very much worse, or severe worsening of rickets) to + 3 (very much better, or complete or near complete healing of rickets).

b. LS mean, SE, CI, and 2-sided p value per ANCOVA model, which included RGI-C as the dependent variable, treatment group and baseline age stratification factor as independent variables and Baseline RSS score as a continuous covariate

c. LS Mean, SE, CI and 2-sided p-value per GEE model, which included RGI-C as the dependent variable, treatment, visit, treatment by visit interaction and baseline age stratification factor as factors, Baseline RSS score as a continuous covariate, with exchangeable covariate structure.

The key secondary efficacy endpoints were change in lower extremity skeletal abnormalities as assessed by the RGI-C long leg score, change from Baseline in standing

height/recumbent length Z score, change from Baseline in RSS total score, change in serum phosphorus from Baseline to mean post baseline values, and change from Baseline in serum ALP levels. There was no multiplicity adjustment for statistical analyses of the key secondary efficacy endpoints. Consequently, all p-values for the pairwise comparisons between the two treatment groups were nominal rather than confirmatory.

The mean RSS total score decreased from Baseline to Week 40 to a greater extent in the burosumab group compared to the active control group (decrease indicating improvement), with the percent mean decrease being 64% in the burosumab group and 23% in the active control group. The mean RSS total score improved further in both treatment groups through to Week 64, with the percent mean decrease from Baseline at Week 64 being 70% in the burosumab group and 32% in the active control group.

Change from Baseline to Week 64 in lower limb deformity, assessed by the RGI-C lower limb deformity score, showed greater healing in the burosumab group compared to the active control group. The improvement in lower limb deformity score in the burosumab group observed at Week 64 was maintained at Week 88, while switching from active control to burosumab after Week 64 resulted in additional improvement at Week 88 (active control switched over to burosumab) compared to Week 64 (active control). In addition, lower extremity skeletal abnormalities, assessed by RGI-C in standing long leg radiographs, showed greater healing in the burosumab group compared to the active control group at Week 64.

Change from Baseline to Week 64 in standing height/recumbent length Z score showed a greater increase in the burosumab group compared to the active control, with minimal further increase through to Week 88 in both the burosumab group and the active control switched over to burosumab group. The results for growth velocity assessed by the Z score were consistent with the results in standing height/recumbent length Z score.

Change in serum phosphorus from Baseline to Week 40 was notably greater in the burosumab group than in the active control group, and the difference was maintained through to Week 64. The improvement in serum phosphorous level observed at Week 64 in the burosumab group was maintained at Week 88, while switching from active control to burosumab after Week 64 resulted in a notable increase in serum phosphorous level at Week 88 (active control switched over to burosumab) compared to Week 64 (active control).

Change in serum ALP from Baseline to Week 40 was notably greater in the burosumab group than in the active control group, and the difference was maintained through to Week 64. The mean percentage reduction in the serum ALP levels from Baseline to Week 40 and Week 64 were 24% and 33%, respectively, in the burosumab group compared to 7% and 5%, respectively, in the active control group. The reduction in serum ALP level observed at Week 64 in the burosumab group was maintained at Week 88 (32%), while switching from active control to burosumab after Week 64 resulted in a notable decrease in serum ALP level from Baseline at Week 88 (29% reduction in the active control which were switched over to burosumab group) compared to Week 64 (5% reduction in the active control group).

Study UX023-CL205 (supportive)

Study UX023-CL205 was a USA-based, multicentre, open label, single arm, Phase II study in children aged one to four years with XLH, who were naive to therapy or had previously received standard therapy with oral phosphate and active vitamin D. The primary efficacy endpoint was the change from Baseline in serum phosphorous. The secondary efficacy endpoints included assessment of rickets, growth, lower extremity deformity, height and serum ALP levels. The study comprised a 64 week treatment period followed by a 96 week extension period.

Eligible subjects were children, between one and four years old, inclusive, with clinical findings consistent with XLH, and a confirmed *PHEX* mutation or variant of uncertain significance. Subjects receiving oral phosphate and active vitamin D therapy discontinued treatment during screening and for the duration of the study.

Subjects received burosumab at a starting dose of 0.8 mg/kg SC once every two weeks. The dose was increased to 1.2 mg/kg at any time during the study when a subject met dosing adjustment criteria.

A total of 13 paediatric subjects aged one to five years were enrolled. All 13 subjects completed the 64 week treatment period, and 12 subjects continued to receive burosumab for an additional 96 weeks during the extension period for a maximum duration of 160 weeks. One subject was withdrawn after transitioning to commercially available burosumab. At Baseline, mean (SD) age was 2.9 (1.15) years (range: 1.2, 4.9 years), male/female subject distribution was nine (69%) out of four (31%), and most subjects were White (12 subjects; 92%). All subjects showed signs of XLH disease at Baseline by multiple measures.

The primary efficacy endpoint was the change from Baseline in serum phosphorus. The mean (SD) phosphorous level increased from 2.51 (0.284) mg/dL to 3.47 (0.485) mg/dL (n = 13) at Week 40. The LSM change from Baseline was 0.96 mg/dL (95% CI: 0.73, 1.19).

The secondary efficacy endpoints were:

- change in rickets as assessed by the RGI-C global score at Weeks 40 and 64;
- change from Baseline in RSS total score at Weeks 40 and 64;
- change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as determined by the RGI-C long leg score at Weeks 40 and 64;
- change in recumbent length/standing height (cm) from Baseline to post treatment study time points, height for age Z scores, and percentiles based on age and gender; and
- change and percentage change from Baseline over time in ALP.

There was substantial healing of rickets at Week 40 (defined as RGI-C score ≥ +2). Least squares means (SE) RGI-C global score at Week 40, the primary assessment time point, was +2.21 (0.071) (nominal $p < 0.0001$, GEE model). Results were sustained at later time points: LSM (SE) RGI-C global scores at Weeks 64, 112, and 160 were +2.23 (0.111), +2.23 (0.076), and +2.14 (0.114), respectively (nominal $p < 0.0001$ at all time points, GEE model).

There was also a reduction in rickets severity at Week 40. Mean (SD) total RSS decreased from 2.92 (1.367) to 1.19 (0.522) at Week 40. Effects were sustained to Week 160. The LSM (SE) change in RSS total score from Baseline to Week 40 was -1.75 (0.116) (nominal $p < 0.0001$, GEE model).

There were improvements in abnormalities observed in long leg radiographs starting at Week 40. LSM (SE) RGI-C lower limb deformity from Baseline to Week 40 was +1.21 (0.155) (nominal $p < 0.0001$, GEE model). Healing of lower limb deformities was sustained at later time points. At Week 40, lower limb deformities present at Baseline (left (L)/right (R) legs) showed improvement for most subjects for the tibia (L/R: 85%/92%) and the femur (L/R: 62%/62%), but improvements were noted less frequently for the fibula (L/R: 29%/29%). At Weeks 112 and 160, all abnormalities present at Baseline in all six lower limb bones showed improvement, with the exception of one subject each for abnormalities in the left and right femur at Week 160.

The mean (SD) increase in recumbent length/standing height from Baseline to Week 160 was 19 (4.21) cm, with a range of 13.6 to 26.6 cm. The mean (SD) recumbent

length/standing height Z score was - 1.54 (1.088) at Week 160: LSM (SE) change from Baseline of - 0.08 (0.183). Changes in recumbent length/standing height Z scores did not significantly differ from Baseline at any time-point during the study (Weeks 40, 64, 112 and 160). Changes in recumbent length/standing height Z scores did not significantly differ from Baseline at any time-point during the study.

Mean (SD) serum total ALP activity decreased from 549 (194) U/L at Baseline to 335 (88) U/L at Week 40. Decreases in serum ALP concentrations were sustained over the course of the study.

Study KRN23-003 (supportive)

Study KRN23-003 is an ongoing, multicentre, open label, single arm, Phase III study designed to assess the PD and safety of burosumab in Japanese children (one to 12 years of age) with XLH. The study included a screening period, a treatment period (through to Week 40), an extended treatment period (through to Week 88), and a follow up period (every 12 Weeks after the last dose). The primary objective of the study was to evaluate the safety of burosumab SC once every two weeks in Japanese children with XLH rickets/osteomalacia. The secondary objectives were to the evaluate effects of burosumab SC once every two weeks on biochemical markers, rickets, motor function, and growth.

Burosumab was administered by SC injection once every two weeks for up to 88 weeks at a starting dose of 0.8 mg/kg. The dose could be escalated up to 1.2 mg/kg according to dose adjustment criteria.

The study enrolled subjects aged ≥ one and ≤ 12 years with a diagnosis of XLH and a *PHEX* mutation identified in either the subject or in a directly related family member with appropriate X-linked inheritance or serum intact FGF23 level at screening ≥ 30 pg/mL. Subjects were required to have radiographic evidence of open growth plates and clinical symptoms of rickets at screening, serum phosphorus levels < 3 mg/dL, serum creatinine levels within the age adjusted normal limits, and serum 25(OH)D levels ≥ 16 ng/mL. Exclusion criteria included height percentile > 50th percentile based on age adjusted Japanese norms at screening. There were also exclusions relating to medications, biochemical parameters, the presence of Grade 4 nephrocalcinosis and planned or recommended orthopaedic surgery during the study period.

Efficacy outcomes were secondary endpoints in this study. The following endpoints were assessed at each time point: changes from Baseline in serum levels of phosphorus, 1,25(OH)2D, and ALP and urinary levels of phosphorus, TRP, and TmP/GFR; improvement in rickets based on the RGI-C global score; changes from Baseline in RSS total score; changes from Baseline in motor function (6 minute walk test) and changes from Baseline in Z score of height (LMS method).

Mean (SD) serum phosphorus level increased from 2.61 (0.32) mg/dL at Baseline to a maximum of 3.73 (0.54) mg/dL at Week 4. Thereafter, there was no marked change in serum phosphorus level. The mean (SD) level at Week 40 was 3.51 (0.45) mg/dL.

Mean (SD) 1,25(OH)2D level increased from 24.65 (12.70) pg/mL at Baseline to a maximum of 70.81 (21.49) pg/mL at Week 1. Thereafter, there was no marked change in 1,25(OH)2D levels. The mean (SD) level was 62.19 (12.50) pg/mL at Week 40.

Mean (SD) ALP decreased from 1589.3 (366.9) U/L at Baseline to 1131.3 (263.6 U/L) at Week 40.

The RGI-C global score was assessed based on findings in the wrists and knees. At Week 40, the mean (SD) RGI-C global score was +1.51 (0.80). The mean (SD) RGI-C leg deformity score was +0.73 (0.85) at Week 40. The mean (SD) baseline RSS total score was +1.29 (1.17) and decreased to + 0.62 (0.58) at Week 40.

Mean (SD) 6 minute walk test increased from 425 (81.3) metres at Baseline to 461.1 (58.2) metres at Week 24 and 437.6 (77.3) metres at Week 40, with the mean increases from Baseline being 24.1 (60.7) metres at Week 24 and 12.6 (75.5) metres at Week 40.

There were no clinically meaningful changes in height based on the Z scores.

Safety

Safety in adults with X-linked hypophosphataemia

Five studies provided evaluable safety data in 175 unique adult subjects with XLH exposed to repeat dose burosumab. Key safety data in adults is provided by pivotal Study UX023-CL303 in 134 subjects treated with burosumab with supporting safety data from Study UX023-CL203 (20 subjects), Study UX023-CL304 (14 subjects), and Study KRN23-INT-001/002 (28 subjects; 20 of these subjects also participated in Study UX023-CL203).

Mean (SE) exposure to burosumab was 771.3 (21.97) days in the burosumab group (143.60 subject years of exposure to burosumab) and 625.7 (19.40) days in the placebo that were switched over to burosumab group (113.07 subject-years of exposure to burosumab). In the total burosumab group (all periods combined), the mean (SE) duration of exposure was 699.6 (15.93) days (range: 165 to 957 days), and the total subject years of exposure to burosumab was 256.67.

In the placebo-controlled treatment period, treatment-emergent adverse events (TEAEs) occurred in 61 (92.4%) subjects in the placebo group and 64 (94.1%) subjects in the burosumab group. The TEAEs considered to be related to study drug were reported in 30 (44.1%) subjects in the burosumab group and 27 (40.9%) subjects in the placebo group. Serious TEAEs were reported in one (1.5%) subject in the placebo group and two (2.9%) subjects in the burosumab group. No TEAEs leading to study discontinuation or treatment discontinuation occurred in either treatment group. The TEAEs reported in ≥ 10% of subjects in the burosumab group versus the placebo group, respectively, were nasopharyngitis, back pain, headache, tooth abscess, dizziness, restless legs syndrome, and nausea. Each of the TEAEs reported in ≥ 10% of subjects occurred more frequently in the burosumab group compared to the placebo-group.

In the total burosumab group, 98.5% of subjects reported TEAEs. The most commonly reported TEAEs in the total burosumab group were consistent with those reported in the burosumab group in the placebo controlled treatment period. Serious TEAEs occurred in 16.4% (n = 22) of subjects. One (0.7%) subject in the total burosumab group had a fatal TEAE.

Most events observed with burosumab were mild or moderate in severity. Eight subjects in each treatment group experienced severe (Grade 3) TEAEs. The only Grade 3 TEAE reported in ≥ one subject in the placebo controlled treatment period was tooth abscess in the burosumab group (three subjects (4.4%), burosumab versus zero subjects (0%), placebo). In the total burosumab group, Grade 3 TEAEs were reported in 40 (29.9%) subjects. No Grade 4 TEAEs were reported. One Grade 5 (fatal) TEAE (road traffic accident) unrelated to treatment occurred in the burosumab group.

Serious TEAEs in the placebo controlled treatment period were reported in two (2.9%) subjects in the burosumab group and one subject in the placebo group but none of these serious TEAEs were considered to be treatment related. Through to the end of study, 22 (16.4%) subjects in the total burosumab group experienced serious TEAEs, with the only events reported in ≥ two subjects being arthralgia (two (1.5%)) and myelopathy (two (1.5%)). Only one serious TEAE was considered to be related to treatment (spinal stenosis). The patient was reported to have an extensive history of spinal column stenosis

and associated spinal surgeries. At the end of the study, all serious TEAEs were assessed as resolved or recovered apart from one event of joint range of motion decreased.

The TEAEs of interest were injection site reactions (ISRs), hypersensitivity, hyperphosphataemia, ectopic mineralisation, and restless legs syndrome (RLS). In the placebo controlled treatment period, ISRs occurred in eight subjects in both treatment groups, hypersensitivity in four subjects in both treatment groups, hyperphosphataemia in four (5.9%) subjects in the burosumab group and no subjects in the placebo group, RLS in six (9.1%) and eight (11.8%) subjects, respectively and ectopic mineralisation occurred in no subjects.

In the total burosumab group through to the end of study, ISRs occurred in 35 (26.1%) subjects, hypersensitivity in 23 (17.2%) subjects, hyperphosphataemia in eight (6%) subjects, ectopic mineralisation in 11 subjects (8.2%), and RLS in 22 (16.4%) subjects. Estimated exposure adjusted incidence for these events of interest were ISRs = 0.64 events/year; hypersensitivity = 0.19 events/year; hyperphosphataemia; ectopic mineralisation in 11 = 0.04 events/year); and RLS = 0.12 events/year). The sponsor's review of cases was not suggestive of an increased risk of ectopic mineralisation with burosumab treatment.

Of the 134 subjects in the total burosumab group, 13 (9.7%) subjects were anti-drug antibody (ADA) positive at any visit after initiation of burosumab, and all ADA samples were negative for neutralising activity. There was no evidence that the presence of ADAs impacted on the safety profile of burosumab in adults.

Elevated serum phosphorus levels either spontaneously normalised or were successfully managed with protocol defined burosumab dose reductions. In the placebo controlled treatment period, nine (13.2%) subjects in the burosumab group had high serum phosphorus levels (> 4.5 mg/dL) at least once, and five of these nine subjects required dose reductions. Subsequent serum phosphorus levels for these subjects remained within the reference range. After initiation of burosumab in the open label treatment continuation period, eight subjects (12.1%) in the placebo which were switched over to burosumab group had high serum phosphorus levels and four of these eight subjects required protocol specified dose reductions. In the treatment extension periods, three subjects had high serum phosphorus levels, but did not require dose reductions.

Safety in children with X-linked hypophosphataemia

Safety data were provided for 135 children with XLH aged one to 12 years. Pivotal Study UX023-CL301 contributed 55 subjects aged one to 12 years, supportive Studies UX023-CL201, UX023-CL205 and KRN23-003 contributed 52 subjects aged five to 12 years, 13 aged one to four years, and 15 aged one to 12 years, respectively. 62 subjects were exposed to burosumab for ≥ three years.

The pivotal safety data were provided by the Study UX023-CL301. The three supportive studies were consistent with the safety data from this pivotal study.

In Study UX023-CL301, overall mean (SD) duration of exposure to burosumab, was 12.82 (7.337) months, with a range of 1.5 to 27.7 months. The total duration of exposure to burosumab for this combined group was 58.76 patient-years. During the 66-week treatment period 100% (29 out of 29) of subjects in the burosumab group and 84.4% (27 out of 32) of subjects in the active control group experienced at least one TEAE. The majority of TEAEs were mild or moderate in severity. Severe TEAEs (Grade 3) were reported in three (9.4%) subjects in the active control group and four (13.8%) subjects in the burosumab group. Serious TEAEs were reported in three (9.4%) and four (13.8%) subjects, respectively.

Serious TEAEs were reported in six subjects: three (10.3%) subjects in the burosumab group (craniosynostosis, viral infection, and migraine), and three (9.4%) subjects in the

active control group (haematuria, craniosynostosis, and knee deformity). The serious events were all mild or moderate in severity, with the exception of craniosynostosis in the active control group (Grade 3). All serious TEAEs required hospitalisation, none were assessed as related to treatment.

For the TEAEs of interest, only ISRs and hypersensitivity reactions were reported. In the burosumab group, 15 (51.7%) subjects experienced ISRs. All events were mild except for one event of moderate severity (injection site rash). In the burosumab group, 11 (37.9%) subjects experienced hypersensitivity reactions compared to six (18.8%) subjects in the active control group. Hypersensitivity TEAEs reported in ≥ 5% of subjects in either treatment group (burosumab versus active control) were rash (10.3% versus 6.3%), injection site rash (10.3% versus 0%), injection site urticaria (6.9% versus 0%), allergic rhinitis (6.9% versus 0%), and hypersensitivity (3.4% versus 6.3%). All hypersensitivity reactions in both treatment groups were categorised as mild or moderate in severity and none were categorised as serious.

In a cumulative dental assessment, at Week 64 dental conditions occurred notably more frequently in subjects in the burosumab group than in the active control group (12 (41.4%) versus five (15.6%)).

In the total burosumab group (safety data Weeks 0 to 164), 89.1% (n = 49) of subjects experienced at least one TEAE. The majority of TEAEs were mild or moderate in severity. Severe (Grade 3) TEAEs were reported in five (9.1%) subjects, but there were no life threatening (Grade 4) or fatal (Grade 5) TEAEs reported.

The most frequently reported TEAEs occurring in ≥ 10% of subjects, in descending order of frequency, were: pyrexia; nasopharyngitis; cough; vomiting; arthralgia; injection site erythema; pain in extremity; headache; rhinorrhoea; tooth abscess; dental caries; injection site reaction; oropharyngeal pain; nasal congestion; diarrhoea; constipation; nausea; vitamin D decreased; toothache; ear pain; and upper abdominal pain.

Severe (Grade 3) TEAEs were reported in five (9.1%) subjects in the total burosumab group (viral gastroenteritis, tooth abscess, papilloedema, ketonuria, arthralgia, dysuria). No life threatening (Grade 4) TEAEs were reported in the total burosumab group.

Serious TEAEs were reported in four (7.3%) subjects in the total burosumab group (craniosynostosis, papilloedema, viral infection and migraine). Of the serious TEAEs, papilloedema was considered by the investigator to be related to treatment with burosumab. This event occurred in a male patient, aged seven years, in the burosumab group who experienced bilateral papilloedema four months after initiating treatment with burosumab. The concurrent medical history included craniostenosis, raised intracranial pressure, photophobia, headaches and vomiting. The investigator considered the event possibly related to treatment, but the sponsor considered the relationship be unlikely and more likely due to the patient's pre-existing history of craniosynostosis.

In the total burosumab group, injection site reactions occurred in 41.8% (n = 23) of subjects. The reactions were all mild or moderate in severity. Hypersensitivity events occurred in 20% (n = 11) of subjects. The events were all mild or moderate in severity. The events were mostly rash related, generally resolved without treatment or with treatment with over the counter medications, and generally did not recur with subsequent burosumab therapy. There were no events for hyperphosphataemia, ectopic mineralisation or RLS.

In the total burosumab group, there were four (7.2%) subjects who tested positive for ADAs during the trial, and one subject who was positive for ADA with a low titre (< 1:2 or 1:2) at Baseline and post-baseline was positive for NAb post baseline. In Study UX023-CL201, a dose finding study in children, serum samples from six (12%) subjects tested positive for anti-burosumab antibodies at Baseline, and samples from two

subjects were positive at every visit. Six (12%) subjects who were negative at Baseline were positive at any post-baseline visit, and two (4%) subjects who were positive at Baseline were negative at any post-baseline visit. Overall, eight (15%) subjects were ADA positive at any post baseline visit. Three (6%) of the ADA positive subjects were positive for NAb during treatment.

Post-market/Early access experience

The submission included two periodic safety update reports (PSURs) covering from 19 February 2019 to 18 February 2020. Since the development international date of birth, 378 subjects have received burosumab in sponsored clinical studies and 2320 patients have been exposed to burosumab through the commercially sold product or an early access program. Post-market reports of adverse drug reactions in adolescent patients were consistent with those reported in the clinical studies in children. No additional safety signals have emerged in adolescents treated with burosumab.

Data from the Australian early access program indicated that 49 paediatric subjects had received burosumab by 24 June 2020. As of 31 May 2020, 42 paediatric subjects had experienced at least one adverse event. Six subjects experienced serious adverse events (limb operation (three), papilloedema (two), blood alkaline phosphatase increased, migraine, removal of internal fixation).

Clinical evaluator's recommendation

The clinical evaluator has recommended that burosumab be approved for the treatment of adults, adolescents and children one year of age or older. The clinical evaluator recommends that burosumab be approved at the dosages proposed by the sponsor for these patient populations.

Risk management plan

The sponsor submitted EU- risk management plan (RMP) version 2.1 (dated 31 March 2020; data lock point (DLP) 18 February 2019) and Australian specific annex (ASA) version 1 (20 July 2020) in support of this application. With the responses to the TGA's questions, the sponsor provided an updated ASA version 1.1 (dated 26 October 2020) which is aligned to EU-RMP version 1 (dated 12 December 2017; DLP 18 July 2017). In response to the second round of TGA's questions, the sponsor provided updated ASA version 1.2 (dated 4 December 2020) which is aligned to EU-RMP version 2.1 (dated 31 March 2020; DLP 18 February 2019). In response to the second round evaluation recommendations, the sponsor submitted updated ASA version 1.3 (dated 26 February 2021) to align with EU-RMP version 2.1 (dated 31 March 2020; DLP 18 February 2019).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7.[9]

[9] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 7: Summary of safety concerns

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

‡ Post-authorisation safety study

The summary of safety concerns is considered acceptable from an RMP perspective.

The sponsor has proposed routine pharmacovigilance for all safety concerns. Additional pharmacovigilance has been proposed in the form of a post authorisation safety study (PASS) in the EU, to address the safety concerns noted in the table above. The pharmacovigilance plan is acceptable from an RMP perspective.

The sponsor has proposed routine risk minimisation activities only for all safety concerns. No additional routine risk minimisation activities have been proposed. The risk minimisation plan is acceptable from an RMP perspective.

Risk-benefit analysis

Delegate's considerations

X-linked hypophosphataemia is a rare, serious, debilitating condition and in Australia, there are no approved therapies for the condition. Conventional therapy with oral phosphate and active vitamin D aims to supplement phosphate but offers limited benefits with respect to skeletal outcomes. In addition, conventional therapy is associated with significant safety concerns such as hyperparathyroidism and nephrocalcinosis and compliance with treatment and monitoring requirements is challenging for patients.

In pivotal Study UXCL23-CL303 in adults, serum phosphorous response was higher with burosumab treatment compared to placebo and the difference was statistically significant.

These levels were maintained through to Week 96. The increase in serum phosphorus with burosumab was also associated with improvements in TmP/GFR though was not a key secondary endpoint. There were modest improvements in the three key secondary efficacy endpoints of worst pain scores (measure by BPI), physical functions scores (measure by WOMAC) and stiffness scores (WOMAC)in subjects treated with burosumab compared to placebo but only the improvement in stiffness score from Baseline was statistically significant, although the difference of approximately eight units was not considered by the evaluator to be clinically meaningful. The percentage of baseline active fractures/pseudofractures graded as fully healed at Week 24 was greater in the burosumab group but this endpoint was exploratory only. In Study UX023-CL303 patients were exposed to burosumab treatment for a maximum of 149 weeks. There were no data regarding sustained benefit or loss of benefit after cessation of treatment.

Supportive Study UX023-CL304 showed burosumab treatment was associated with a mean reduction in osteoid volume. There was no control group for comparison but osteoid volume is not expected to improve. There were also improvements in additional osteomalacia parameters with burosumab treatment.

In pivotal Study UX023-CL301 in children one to ≤ 12 years of age, burosumab treatment was associated with statistically significantly greater healing of rickets compared to the active control group at Week 40 (LSM difference = 1.14 (95% CI: 0.83, 1.45), $p < 0.0001$). Greater healing was also observed in RGI-C knee and wrist scores. Changes in mean RSS scores were consistent with those for RGC-I scores. Improvements in standing long leg radiographic abnormalities were greater at Weeks 40 and 64. Improvements in height/recumbent length Z scores and growth velocity were generally consistent with improvements in long leg radiographic abnormalities assessed by RGI-C scores. In children aged ≥ five years, walking ability assessed by the 6 minute walk test increased from Baseline to Weeks 40 and 64 to a greater extent in the burosumab group compared to placebo. In children aged ≥ five years, improvements in the Patient Reported Outcome Measurement Information System (PROMIS) pain interference, physical function and fatigue domain scores favoured the burosumab group.

The submission presents data from 175 adults and 135 children aged one to 12 treated with burosumab for XLH. The risks of burosumab treatment in adults with XLH are considered to be acceptable, based on the safety data in Study UX023-CL303 with no new safety signals identified in the open label treatment or treatment continuation or extension periods. Limitations of the safety data include the lack of data in subjects treated for three years or more. The optimal duration of treatment in adults not known but is anticipated to be long term. In addition, adult trial subjects in Study UX023-CL303 had significant morbidity associated with XLH and it is uncertain whether individuals with less severe disease would derive a similar benefit from burosumab therapy.

The safety profile of burosumab treatment in children with XLH was satisfactorily demonstrated. The major safety concerns with burosumab treatment in children related to injection site reactions, hypersensitivity reactions and dental abscess. Similar to the concerns outlined above for adult patients, it is uncertain how long treatment with burosumab should continue. There are no clinical data for children as they transition to adults and no data for children who recommence burosumab therapy as adults. Children included in the study had significant radiographic evidence of bone disease, it is unclear whether children with less severe disease would receive similar benefits from burosumab treatment.

The Delegate had concerns regarding the limited data available for adolescent patients (aged 13 to 17 years). Despite the lack of trial data for adolescent patients, the extrapolation of efficacy and safety from the adult and paediatric population is likely acceptable. However, it is unclear whether the choice of dosing regimen is optimal and whether the transition to adult dosing should occur earlier than the recommended

18 years of age. The recommended starting does in this patient population is 0.8 mg/kg once every two weeks, which can be titrated up to a dose of 2 mg/kg once every two weeks to achieve the target phosphorous level. This is the same dosing regimen as that proposed for children (one to 12 years). The adolescent dosing regimen was selected based on modelling and simulations using interpolation between the adult and paediatric XLH populations. Burosumab exposure estimates are predicted to be greater following burosumab 0.8 mg/kg once every two weeks dosing relative to burosumab 1 mg/kg once every four weeks dosing, with C_{min}, C_{avg}, and C_{max} being 2.11-fold, 1.57-fold, and 1.31-fold greater, respectively. The predicted increases in serum burosumab exposure for once every two weeks dosing relative to once every four weeks dosing translate into predicted increases from Baseline in serum phosphorus C_{min}, C_{avg}, and C_{max} of approximately 1.44-fold, 1.13-fold, and 1.23-fold, respectively. The sponsor considers the once every two weeks regimen to offer advantages of greater burosumab and serum phosphorus levels in adolescent patients given the greater rate of growth from 12 to 17 years of age relative to adults greater burosumab exposures and greater serum phosphorus levels, with reduced variability in burosumab exposures. The sponsor considers the benefit of greater exposures and less variability in peak to trough burosumab levels to be important for growing adolescent patients. By the age of 18 years, the importance of these factors is lower as bone growth and maturity begins to slow relative to the early adolescent development. Adolescents transition from the paediatric dosing regimen to the adult dosing regimen of 1 mg/kg once every four weeks at 18 years. The transition and associated initial decrease in exposure may result in reductions in serum phosphorus exposure parameters. It will take an estimated three months to achieve a new serum burosumab steady state following the change from once every two weeks to once every four weeks dosing. Once this new burosumab steady state level is reached, serum phosphorus levels are expected to achieve and maintain the targeted range.

The Delegate seeks the Committee's advice as to whether a statement in the Crysvita Product Information (PI) recommending the use of contraception in women of childbearing age is warranted. The RMP evaluator requested the proposed PI include such a statement after noting that European Union Summary of Product Characteristics states '*Crysvita is not recommended during pregnancy and in women of childbearing potential not using contraception*'.[10] A similar statement is not included in the United States of American Product Information or Health Canada Product Monographs. The nonclinical evaluator did not consider a statement to this effect necessary given the level of concern arising from the animal data. The proposed PI states that burosumab is not recommended for use in pregnancy. The Delegate suggests including a statement that contraception be considered in sexually active women and adolescents although this is not a standard statement for Pregnancy Category B3 medicines.[6]

The proposed PI allows for the initiation of treatment by non specialist practitioners. The EU summary of product characteristics includes a statement limiting the initiation of treatment to physicians experienced in the management of patients with metabolic bone disease. A similar statement is that also includes the monitoring of patients is included in the indications in the indications in the Health Canada product monographs (see Table 1). The Delegate suggested including a statement in section 4.2 of the PI restricting the initiation and supervision of treatment to specialist medical practitioners experienced in the management of patients with metabolic bone disease.

[10] EMA, European Public Assessment Report (EPAR), Crysvita (burosumab), EMEA/H/C/004275-IA/0027/G, 3 December 2021. Available from the EMA website.

Proposed action

Subject to committee advice, the Delegate's preliminary view tends towards a favourable benefit-risk profile for Crysvita (burosumab) for the treatment of XLH in adult, adolescent and paediatric patients one year of age or older.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please provide an update on the current international regulatory status of similar submissions overseas? Have the submission been rejected, withdrawn or deferred in any country or region?***

The sponsor provided the updated international regulatory status as per below (Table 8). There has been no rejection, withdrawal, or deferral for the burosumab submission so far.

Table 8: International regulatory status of selected countries

Region	Submission date	Status	Approved indications
European Union (EU)– centralised procedure	30 November 2016	Approved on 19 February 2018	*The treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children one year of age and older and adolescents with growing skeletons*
	27 August 2019	Approved 30 September 2020	*The treatment of XLH, in children and adolescents aged one to 17 years with radiographic evidence of bone disease, and in adults*
	17 December 2020	Pending	*The treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged one year and over*

Region	Submission date	Status	Approved indications
USA	17 August 2017	Approved on 17 April 2018	*The treatment of XLH in adult and paediatric patients one year of age and older*
	11 December 2018 29 March 2019	Approved 27 September 2019	*The treatment of XLH in adult and paediatric patients six months of age and older*
	18 December 2019	Approved on 18 June 2020	*The treatment of FGF23-related hypophosphataemia in TIO associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in adult and paediatric patients two years of age and older*
Canada	11 May 2018	Approved on 5 December 2018	*The treatment of XLH in adult and paediatric patients one year of age and older*
	28 June 2019	Approved on 16 June 2020	*The treatment of XLH in adult and paediatric patients six months of age and older*
	1 February	Pending	*The treatment of FGF23-related hypophosphataemia in TIO associated with tumours that cannot be curatively resected or localised in adult and paediatric patients one year of age and older*

Region	Submission date	Status	Approved indications
Japan	7 January 2019	Approved on 20 September 2019	*FGF23-related hypophosphataemic rickets and osteomalacia*
Switzerland	31 August 2018	Approved on 20 January 2020	*The treatment of XLH in adults, adolescents and children one year of age and older*
Singapore	24 September 2019	Pending	*The treatment of XLH in adult and paediatric patients one year of age and older*

2. The proposed PI indicates burosumab is intended for administration by a healthcare provider. It is noted that Study KRN23-003 assessed the feasibility of self-administration or administration by a family member. Does the sponsor intend to accommodate administration by a non-professional in the future?

The sponsor has not yet decided whether to accommodate the administration by a non-professional at this time. In the future, the sponsor may consider this based on the medical needs of patients in each region.

3. Will the planned post-authorisation safety studies (PASS) or post-market data examine the long-term effects of burosumab treatment with respect to bone mineral density, nephrocalcinosis or dental health?

The long term effects of burosumab treatment will be examined via routine and additional pharmacovigilance activities. Additional pharmacovigilance activities being conducted are the PASS in the EU and a XLH Disease Monitoring Program in North America and Latin America.

Post marketing routine pharmacovigilance is conducted according to regulatory requirements. Core procedures for routine pharmacovigilance practices for continuous monitoring and update of the safety profile include the following:

- Evaluation of individual case safety reports from all reporting sources.
- Review of aggregate safety data from all available sources.
- Signal detection.
- Review of scientific literature with possible implication for product safety.
- Safety reporting to regulatory authorities in accordance with applicable regulation/legislation.
- Preparation of aggregate reports as required by legislation.
- Provision of comprehensive information to health professionals via the Product Information.

The sponsor signal detection activities are comprised of periodic signal detection, weekly review of case listing and ad-hoc review of safety information from other sources (for

example, regulatory authorities, partners). For the purpose of periodic signal detection all safety data is being evaluated including but not limited to all individual case safety reports collected worldwide and published literature. During the periodic signal detection, the sponsor reviews all data received worldwide in connection to the safety concerns and the missing information in the RMP.

Nephrocalcinosis is routinely reviewed as part of the risk of ectopic mineralisation. Dental events and any change in bone mineral density, when reported as adverse events (AEs), are being captured in the safety database and will be evaluated as part of routine signal detection.

As mentioned above, the sponsor is conducting additional pharmacovigilance activities to gather further information on long-term use of burosumab.

An XLH registry has been established in the EU and European Economic Area (EEA) to collect natural history data for XLH, to characterise the treatment, progression and long-term outcomes of XLH in patients of all age groups. The EU XLH PASS will use the data collected in the registry. The objectives of the EU XLH PASS are below:

- Primary objectives:
  - To evaluate the frequency and severity of safety outcomes in children and adolescents aged one to 17 years with radiographic evidence of bone disease, and adults, treated with burosumab, including but not limited to: death, hospitalisations, cardiovascular disease, cancer, hyperphosphatemia and its complications, ectopic mineralisation (which includes nephrocalcinosis) and increased parathyroid hormone levels;
  - To prospectively evaluate the frequency and outcomes of pregnancies in female patients treated with burosumab.
  - To prospectively evaluate the frequency and severity of safety outcomes in patients with mild to moderate chronic kidney disease at Baseline treated with burosumab
- Secondary objective:
  - To perform a retrospective cohort study using data from the registry to compare the safety outcomes of interest in patients exposed to burosumab to those in patients receiving alternative treatments for XLH.

The EU XLH PASS objectives are safety objectives and long-term effects of burosumab treatment with respect to bone mineral density and dental health will be evaluated as safety outcomes when reported as adverse events.

An XLH disease monitoring program has been established in North America (including Canada) and Latin America (Argentina, Brazil, Canada, Chile, Colombia); it is a global, observational, prospective, multicentre, longitudinal, long term outcomes program for subjects on or off treatment designed to characterise XLH disease presentation and progression, assess long term safety and effectiveness of burosumab, as well as prospectively investigate longitudinal change over time across biomarker(s), clinical assessments, and patient/caregiver-reported outcome measures in a representative population. The objectives of the XLH disease monitoring program are:

- To assess the long-term safety of burosumab treatment in adult and paediatric patients with XLH, including overall renal health, the presence and/or progression of nephrocalcinosis and spinal stenosis, and pregnancy outcomes
- To evaluate the long-term effectiveness of burosumab treatment on key manifestations of XLH, including skeletal health, stiffness, mobility and physical functioning

- To illustrate the clinical, radiological, biochemical manifestations and progression of XLH over time in both untreated and treated patients with XLH

Currently, there is no evidence that the safety profile will be different with long-term use when compared with that of short-term use.

Advisory Committee considerations[11]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Does the committee consider it reasonable to extrapolate the paediatric dosing regimen to the adolescent population?

The ACM advised that it is reasonable to extrapolate the paediatric dosing regimen to the adolescent population, with monitoring and adjustment of dose according to biochemical response. In providing this advice, the ACM considered that while there were no adolescents included in the trials, there is some post-market experience in adolescent patients as per the periodic safety update report. The ACM also reasoned that linear growth and bone mass accrual are both occurring at an increased rate during puberty.

The ACM was of the view that 17 years of age is a reasonable cut-off to extrapolate the paediatric dosing, as there is almost complete epiphyseal fusion by 17 years of age at a population level.

2. Does the committee think that contraceptive advice should be included in the PI for sexually active women and adolescents?

The ACM was of the view that the evidence thus far indicates that getting pregnant while on burosumab is not contraindicated, and discussed that, in theory, the high molecular weight of burosumab means that it will not cross the placenta in the first two trimesters of human pregnancy. However, they advised it seems reasonable to exercise some degree of caution due to the lack of human pregnancy or breastfeeding data. As such, they advised that a statement should be included in the PI that sexually active women and adolescents taking burosumab should consider the use of appropriate contraception and discuss this with their healthcare provider to assist in weighing up the individual risks and benefits.

In providing this advice, the ACM noted that the condition of XLH itself is linked with complications during pregnancy, and female patients with this condition should have counselling regarding contraception and pregnancy, regardless of whether they are using burosumab.

3. The Delegate proposes to limit the initiation and monitoring of burosumab treatment to medical specialists with experience in the diagnosis and management of patients with XLH. Is this reasonable in the context of the likely use of burosumab in clinical practice?

The ACM agreed that the initiation and monitoring of burosumab treatment should be limited to medical specialists with experience in the diagnosis and management of patients with XLH, as this is a highly complex condition with evolving needs and cannot be appropriately managed without expert advice. In remote or resource-limited areas, the ACM advised that initiation and monitoring of burosumab treatment could only occur

[11] The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

under the supervision of a local GP or general specialist in consultation with the appropriate expert in XLH, through mechanisms such as telehealth.

The ACM discussed various methods of diagnosing XLH, including genetic testing, raised FGF23, and hypophosphataemia, and whether such diagnostic criteria should be stipulated in the indication or another section of the PI. The ACM advised that if initiation and monitoring of burosumab is limited to medical specialists with experience in the diagnosis and management of patients with XLH, there is no need to stipulate how the condition should be diagnosed as the specialists have the relevant expertise in identifying and diagnosing the condition.

4. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM expressed concern that there is a lack of information in the PI regarding dose reduction with kidney dysfunction, particularly given the condition of XLH is associated with issues with kidney function. The ACM advised that a statement should be added to the PI that caution should be exercised where patients have an eGFR less than 30 mL/min. The drug has not been tested where eGFR is less than 30 mL/min. The main concern with the use of burosumab is not necessarily drug toxicity, but rather the marked increased risk of hyperphosphataemia, and associated comorbidities. As such, regular monitoring of serum phosphate is of increased importance in the presence of renal impairment.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Crysvita (burosumab) is indicated for the treatment of X-linked hypophosphataemia (XLH) in adults, adolescents and children 1 year of age or older.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Crysvita (burosumab) 10 mg/mL, 20 mg/mL and 30 mg/mL, solution for injection, vial, indicated for:

> *Crysvita (burosumab) is indicated for the treatment of X-linked hypophosphataemia (XLH) in adults, adolescents and children 1 year of age or older.*

Specific conditions of registration applying to these goods

- Crysvita (burosumab) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Crysvita must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Crysvita EU-RMP (version 2.1, dated 31 March 2020; data lock point 18 February 2019), with ASA (version 1.3, dated 26 February 2021), included with submission PM-2020-03892-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (revision 1), Part VII.B structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Laboratory testing & compliance with Certified Product Details
  - All batches of Crysvita supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

  Certified Product Details

  The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.
- The sponsor is required to update the relevant Good Manufacturing Practice (GMP) clearances to reflect the appropriate steps in the manufacturing process included in the ARTG record. This could be done at the next time a GMP clearance is required but should be completed within the next 12 months.
- For all injectable products the Product Information must be included with the product as a package insert

Attachment 1. Product Information

The PI for Crysvita approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au