5.02 BUROSUMAB,
Injection 10 mg in 1 mL, Injection 20 mg in 1 mL, Injection 30 mg in 1 mL
Crysvita®
Kyowa Kirin Australia Pty Ltd

1 Purpose of submission

1.1 The submission requested a Section 100 (S100) – Highly Specialised Drugs Program listing for burosumab, for the treatment of paediatric patients with X-linked hypophosphataemia (XLH).

1.2 Listing was requested on the basis of a cost-utility analysis versus conventional therapy (oral phosphorus and active vitamin D (calcitriol)).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Paediatric patients (< 18 years) with a confirmed diagnosis of X-linked hypophosphataemia
Intervention	Burosumab 0.8 mg/kg (rounded to nearest 10 mg) with upwards/downwards titration according to the PI#, administered every two weeks by subcutaneous injection. Treatment by or in consultation with a paediatric endocrinologist or paediatric nephrologist and administration by a healthcare professional.
Comparator	Current conventional therapy: multiple daily oral doses of phosphorus and calcitriol*
Outcomes	Pharmacodynamic: serum phosphorus, TmP/GFR, 1,25(OH)2D, ALP, TRP and others Clinical: Rickets severity as measured by RSS and RGI-C and growth (in children with growing skeletons). Functional: 6MWT Patient relevant: PROMIS, SF-10 Safety: Incidence and severity of AEs Extrapolated: utilities, rates of surgery, other healthcare utilisation
Clinical claim	Burosumab is superior to conventional therapy in terms of efficacy and safety.

Source: Table 1-1, p14 of the submission.

Abbreviations: 1,25(OH)2D=1,25-dihydroxyvitamin D; 6MWT=six-minute walk test; AE=adverse event; ALP=alkaline phosphatase; PROMIS=Patient-Reported Outcomes Measurement Information System; RGI-C=Radiographic Global Impression of Change; RSS=Rickets Severity Score; SF-10=SF-10 Health Survey for Children; TmP/GFR=ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR); TPR=tubular phosphate reabsorption, PI=product information.

Titrated in increments of 0.4 mg/kg up to a maximum of 2 mg/kg (or 90 mg in total) based on serum phosphorus levels.

* In Section 1 of the submission, the dosing regimen for phosphorus and calcitriol was not provided. In Section 3, conventional therapy comprised 4 x 500 mg effervescent phosphorus tablets and 25 nanogram/kg of calcitriol (p121 of the submission).

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC parallel process. Burosumab has received orphan drug designation and priority review status by the TGA.

2.2 The PBAC noted that the Delegate's overview was received in March 2021, with the proposed TGA indication being: "Crysvita® is indicated for the treatment of X-linked hypophosphataemia (XLH) in adults, adolescents and children 1 year of age or older."

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

Table 2: Essential components of the requested PBS listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity		Proprietary name and manufacturer
				Published:	Effective:	
BUROSUMAB 10 mg in 1 mL*	2	2	5	$15,768.00 (public) $15,815.74 (private)	$[redacted] (public) $[redacted] (private)	Crysvita® Kyowa Kirin Australia Pty Ltd
BUROSUMAB 20 mg in 1 mL*				$31,536.00 (public) $31,583.74 (private)	$[redacted] (public) $[redacted] (private)	
BUROSUMAB 30 mg in 1 mL*				$47,304.00 (public) $47,351.74 (private)	$[redacted] (public) $[redacted] (private)	

Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	☒Medical Practitioners
Episodicity:	Chronic
Severity:	NA
Condition:	X-Linked Hypophosphataemia
PBS Indication:	X-Linked Hypophosphataemia
Treatment phase:	Initial and Continuing
Restriction:	☒Authority Required - In Writing
Treatment criteria:	Patient must be treated by or under the supervision of a paediatric endocrinologist OR Patient must be treated by or under the supervision of a paediatric nephrologist.
Clinical criteria:	A diagnosis of X-linked hypophosphataemia must be confirmed in the patient's medical records.
Population criteria:	Patient must be aged less than 18 years
Prescriber Instructions:	At the time of authority application, medical practitioners must request the appropriate number of vials of appropriate strength to provide sufficient drug, based on the weight of the patient, for one administration. A separate authority prescription form must be completed for each strength requested. Up to a maximum of 3 items will be authorised for any 1 administration.

Source: Tables 1-4 & 1-5, p24 of the submission.

* The submission erroneously indicated in Table 1-4 that burosumab 10/20/30 mg vials were 5 mL, however, the draft PI and other information states burosumab vials contain 1 mL of solution.

3.1 The requested PBS listing for burosumab in children < 18 years of age does not align with the proposed TGA population (adults and children ≥ 1 years of age). Studies supporting the submission enrolled children aged between 1 and 12 years; however, burosumab has also been trialled in adult populations (e.g. Insogna et al 2018)[1] and

[1] Insogna, K.L., Briot, K., Imel, E.A., Kamenický, P., Ruppe, M.D., Portale, A.A., Weber, T., Pitukcheewanont, P., Cheong, H.I., Jan de Beur, S., Imanishi, Y., Ito, N., Lachmann, R.H., Tanaka, H., Perwad, F., Zhang, L., Chen, C.-Y., Theodore-Oklota, C., Mealiffe, M., San Martin, J., Carpenter, T.O. and (2018), A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis. J Bone Miner Res, 33: 1383-1393.

an open label, non-randomised study is underway to evaluate safety, pharmacodynamics and activity of burosumab in children with XLH from birth to 1 year of age (CL207). There is a lack of data informing safety and efficacy in children < 1 year of age and between 13 and 17 years of age (inclusive). The Pre-Sub-Committee Response (PSCR) stated that although the optimal clinical place in therapy for burosumab would ultimately be as chronic therapy for any patient with a confirmed diagnosis of XLH, irrespective of age, it is paediatric patients who have the greatest clinical need and potential for benefit with burosumab treatment. The PSCR further proposed then expanding PBS access with any extensions to the target population on their merits, as clinical experience/understanding, and evidence of effectiveness, safety and cost effectiveness mature.

3.2 A simple clinical criterion was proposed in the restriction: 'confirmed XLH in the patient's medical records', without mention of recent clinical, radiographic or genetic information to support a XLH diagnosis. The submission justified this by stating that the diagnosis of XLH is multifactorial with no single observation or test, and is already routine clinical practice in Australia. To ensure appropriate use and alignment with the clinical evidence of burosumab, the evaluation suggested the PBAC may wish to seek confirmatory evidence of diagnosis, which may include: serum phosphate levels, evidence of normal renal function, radiographic evidence of rickets and/or rickets severity, age criteria and confirmation of XLH via PHEX mutation testing (which was an inclusion criterion in all the clinical studies presented in the submission). If genetic confirmation of PHEX pathogenic variant is deemed necessary, then it might be appropriate for the sponsor to cover the cost of that testing. The Canadian Agency for Drugs and Technologies in Health (CADTH) [2] recommended burosumab for listing provided patients satisfy specific initiation and continuation criteria (including genetic testing). The PSCR reiterated that diagnosis of XLH is multifactorial, involving various clinical assessments, laboratory and radiological investigations, family history and genetic and immunogenic tests, with no single observation being definitive. The PSCR stated that the recommended diagnostic workup for XLH, including PHEX testing, is routine in most Australian treatment centres and unlikely to change. The PSCR also noted that there are relevant mutations of the PHEX gene which are not captured by currently available tests and that an eligibility requirement for a positive PHEX mutation test may inappropriately exclude patients with a diagnosis confirmed by methods other than genetic analysis. The PBAC recommended that the restriction include more clinically based criteria beyond 'confirmed XLH in the patient's medical records' such as serum phosphate levels and radiographic evidence of rickets and include confirmation of a PHEX pathogenic variant.

[2] CADTH Common Drug Review: Canadian Drug Expert Committee Recommendation, Burosumab. May 2020.

3.3 Population criteria for the PBS restriction stated patients must be < 18 years. This age limit was selected in preference to a more clinically orientated criterion such as prior to closure of growth plates (epiphyseal closure) which would allow use to continue in adolescents with growing skeletons. Benefits of burosumab for rickets and establishment of height diminish after growth plate closure. The submission justified the age cut-off arguing it is sufficient to enable access to treatment for patients with variable growth potential and to provide equitability between sexes. Sex differences indicate that epiphyseal closure may occur earlier in girls than in boys (15 vs 17 years, respectively), and that in some adolescents, epiphyseal closure may occur beyond 18 years of age. On this basis, a more objective criteria such as 'prior to epiphyseal closure' may be preferred, or alternatively, use of both criteria (age cut off and epiphyseal closure whichever occurs first) may be appropriate if an age-restricted listing was to be pursued. The PSCR stated that the appropriate cut-offs for the initial target population were open to debate and that the age and clinical criteria of the proposed restriction presented in the submission were a pragmatic starting point and that more clinically based eligibility criteria, including concepts such as epiphyseal closure or skeletal growth have been employed in other jurisdictions. The majority of rickets and growth efficacy effects are seen in children and adolescents; however, the ESC noted that, although the efficacy was uncertain, burosumab appeared to have continued benefits in adults in terms of normalisation of serum phosphate levels, improved physical functioning, fracture healing and reduced stiffness (Insogna et al 2018). The PBAC considered a single PBS listing covering all ages (consistent with the TGA indication), with a broadening of prescribers to cover the adult population, was preferred.

3.4 The submission did not propose any continuation criteria for burosumab, which may not be appropriate. There is a lack of long term follow up data in the presented clinical studies to determine long term benefit of burosumab (see Comparative Effectiveness). To ensure patients continue to benefit from burosumab, the evaluation suggested the PBAC may wish to consider continuation criteria such as: annual review of rickets (versus baseline initially then ongoing assessment for maintained improvements) and review of worsening clinical symptoms of XLH such hyperparathyroidism, nephrocalcinosis, or evidence of fracture or pseudofracture based on radiographic assessment. The ESC agreed with the PSCR which stated that any continuation criteria would need to reflect the maintained effects of burosumab, rather than require ongoing year-on-year improvement. The PBAC considered that the ESC's advice was reasonable.

3.5 There are < 500 patients currently enrolled in an Early Access Program (EAP) for burosumab in Australia. A Grandfathering restriction was not requested for these patients as they currently meet the proposed restriction. The PBAC considered that a Grandfathering clause would be required.

3.6 The sponsor requested a S100 – Highly Specialised Drugs Program (public and private hospitals) - Authority Required (Written) listing of burosumab 10 mg, 20 mg and 30 mg vials on the basis that XLH is a rare and complex condition requiring medical specialist management (usually in public hospitals). By way of precedent, the submission noted several other S100 listed drugs for paediatric conditions: adalimumab/tocilizumab (subcutaneous administration with autoinjector pen) for severe active juvenile idiopathic arthritis, anakinra (subcutaneous administration) for cryopyrin associated periodic syndrome and ivacaftor (oral administration) for cystic fibrosis. The need for assisted administration (the pack does not come with an easy to use injector) could make it difficult for those in remote or rural areas to attend a hospital on a fortnightly basis to receive injections. The PBAC considered that a Section 100 listing would be appropriate for initial and continuing supply.

3.7 A special pricing arrangement (SPA), which consisted of a [redacted]% rebate of the published approved ex-manufacturer price (AEMP) for each vial strength, was proposed.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 XLH is a rare, lifelong and progressive, X-linked inherited disorder characterised by low levels of phosphate in the blood. XLH is caused by mutations on the X chromosome (PHEX) gene. Excess levels of circulating fibroblast growth factor 23 (FGF23) result in reduced renal phosphate reabsorption and decreased production of active vitamin D leading to chronic hypophosphataemia. This leads to abnormal bone and tooth mineralisation, and debilitating musculoskeletal deficits. XLH usually manifests and is diagnosed during the first two years of life. In children, XLH causes osteomalacia and rickets, which can lead to lower-limb deformities, bowed or bent legs, stunted growth, and less commonly, cranial synostosis. Patients also experience spontaneous dental abscesses and occasionally sensorineural hearing deficit. Clinical manifestations of XLH in children lead to impaired mobility and physical function. Children experience delayed walking, waddling gait, bone pain and fatigue. Skeletal abnormalities and short stature acquired in childhood become irreversible after the completion of growth. Together, these factors, lead to emotional and social detriments, and reduced quality of life. The population targeted in the submission included patients < 18 years of age with XLH. Burosumab is expected to improve rickets and growth (height) in children and adolescents with growing skeletons; these effects diminish once growth plates are closed (epiphyseal closure), although there are other benefits of burosumab in adults such as normalisation of serum phosphate levels, improving physical functioning and reducing pain and stiffness. There is no clinical trial evidence for burosumab in children aged 13 to 17 years (inclusive).

4.2 Burosumab is a recombinant human monoclonal antibody (immunoglobulin G subclass (IgG1)) that binds to and inhibits the activity of fibroblast growth factor 23

(FGF23). By blocking FGF23 activity, there is increased renal tubular reabsorption of phosphate and serum concentration of 1,25 dihydroxy-Vitamin D, which has shown to lead to improvements in bone mineral metabolism and healing of rickets, thereby increasing growth, mobility, and physical functioning.

4.3 It is proposed that burosumab would replace conventional therapy (oral phosphorus and calcitriol) as a treatment option in eligible patients, thus the main difference between current and proposed clinical management algorithms was simply the inclusion of burosumab as a treatment option. The submission stated that in an ideal world, burosumab use should also be extended to adults (not requested). Serum phosphate testing is required every 4 weeks during the first 3 months of burosumab treatment and periodically thereafter; this monitoring was not included in the clinical management algorithm. The PSCR confirmed that the monitoring regimen is specified in the draft TGA Product Information and is similar to monitoring recommended for conventional therapy and routine follow-up of patients with XLH.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated conventional therapy (oral phosphorus and calcitriol) as the comparator. The PBAC considered this was appropriate.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, described the symptoms of XLH, how burosumab would be used in practice, and how it would improve patients quality of life. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from a large number of individuals (148), health care professionals (9) and organisations (3) via the Consumer Comments facility on the PBS website. Of the comments from individuals, the PBAC noted several were from individuals living with XLH, or supporting someone with XLH, who had direct experience of using burosumab. The comments described a range of benefits of treatment with burosumab including the ease of administration compared to currently available therapies, the effectiveness of the treatment, the tolerability of the treatment and the improved quality of life associated with the treatment. The PBAC also considered input from representatives of XLH Australia Incorporated that had

been summarised by the Consumer Evidence and Engagement Unit of the Department of Health. This input outlined the impact of the condition on gross motor skills, mental health as well as issues around oral health, pain and need for corrective surgery. The PBAC also noted that the consumer input was strongly supportive of a broad PBS listing across all ages, including adults with XLH.

6.3 The PBAC noted the advice received from the National Paediatric Medicines Forum (NPMF), the Australian and New Zealand Bone and Mineral Society (ANZBMS) and the Australasian Paediatric Endocrine Group (APEG) strongly supporting the use of burosumab in clinical practice. The PBAC specifically noted the advice that the use of burosumab may reverse the serious disabilities associated with XLH and significantly improve quality of life. The PBAC noted that this advice complemented the evidence provided in the submission, although the benefit appeared to be greater for the radiological rather than patient reported outcomes in the trials.

Clinical studies

6.4 The submission was based on one head-to-head randomised trial (CL301) comparing burosumab to conventional therapy (oral phosphorus plus calcitriol) and two non-comparative studies (CL201 and CL205) as supportive evidence. CL201 was a dose finding study of burosumab in patients who were treatment naïve or had previously received conventional therapy.

6.5 Details of the studies presented in the submission are provided in Table 3 below.

Table 3: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CL301 NCT02915705	UX023-CL301 Clinical Study Report (End of Study (EOS); up to 124 weeks) A Randomized, Open-Label, Phase 3 Study to Assess the Efficacy and Safety of KRN23 Versus Oral Phosphate and Active Vitamin D Treatment in Pediatric Patients with X-linked Hypophosphatemia (XLH).	16 December 2019
	Imel E, Glorieux FH, Whyte MP, et al. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: a randomised, active-controlled, open-label, phase 3 trial.	The Lancet 2019; 393(10189):2416-2427
CL201 NCT02163577	UX023-CL201 Clinical Study Report (EOS, Week 160): A Randomized, Open-Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 Antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH).	5 April 2019
	Carpenter T, Whyte M, Imel E, et al. Burosumab Therapy in Children with X-Linked Hypophosphatemia.	New England Journal of Medicine 2018; 378(21):1987-1998
CL205 NCT02750618	UX023-CL205 Clinical Study Report (Week 64, EOS): An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics, and Efficacy of KRN23 in Children from 1 to 4 Years Old with X-linked Hypophosphatemia (XLH).	24 January 2020
	Whyte M, Carpenter T, Gottesman G, et al. Efficacy and safety of burosumab in children aged 1–4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial.	The Lancet Diabetes & Endocrinology 2019; 7(3):189-199.

Source: Table 2.2, p31 of the submission.

6.6 The literature search identified one ongoing Phase 3, open-label, single arm, randomised study (KRN23-003, NCT02750618) of burosumab treatment in children aged 1 to 12 years with XLH, which was excluded in the submission on the grounds that administration of the study treatment by self-administration was not consistent with the draft PI (i.e. burosumab should be administered by a healthcare provider). The study assesses the safety, pharmacodynamics (PD) and efficacy of self-administering burosumab every 2 weeks, and is potentially relevant given it reported comparable outcomes in paediatrics with XLH (see paragraph 6.26 for a summary of results from this study).

6.7 The key features of the main studies are summarised in Table 4 below.

Table 4: Key features of the included evidence

Trial	N	Design/duration	Bias	Treatment arms	Population	Outcome(s)	Modelled evaluation
Burosumab vs conventional therapy (oral phosphorus plus calcitriol)							
CL301	61	R, MC, OL, 64 wks (OL extension, results up to 88 wks[e])	Low-moderate	Burosumab 0.8 mg/kg Q2W[a] Conventional therapy[b]	Age 1-12; XLH	1°: RGI-C (Wk 40) 2°: RSS, growth Other: 6MWT, PD, QoL, AEs	RSS
Supportive studies							
CL201	52	R, MC, OL, parallel 64 wks (OL extension, results up to 160 wks for efficacy & 214 wks for safety)	Low-moderate	Burosumab 0.1/0.2/0.3 mg/kg Q2W[c] Burosumab 0.2/0.4/0.6 mg/kg Q4W[c]	Age 5-12; XLH	1°: RSS (Wk 40) 2°: RGI-C, growth, 6MWT Other: PD, QoL, AEs	RSS
CL205	13	MC, OL 64 wks (OL extension, results up to 160 wks)	Low-moderate	Burosumab 0.8 mg/kg Q2W[d]	Age 1-4; XLH	1°: serum phosphorus (Wk 40) 2°: RGI-C, RSS Other: PD, AEs	RSS

Source: Sections 2.3.1.1 to 2.3.1.3, pp34-36 of the submission.

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; R=randomised; RGI-C=Radiographic Global Impression of Change; RSS=Rickets Severity Score; XLH=X-linked hypophosphataemia; 6MWT=Six-minute Walk Test; Q2W=every 2 weeks; Q4W=every 4 weeks; wk(s)=week(s);

a Burosumab initiated at 0·8 mg/kg Q2W injected subcutaneously by a health-care professional at the study site or during a home health visit, and increased to 1·2 mg/kg Q2W if two consecutive pre-dose fasting serum phosphorus concentrations were <1.03 mmol/L (3.2 mg/dL) and serum phosphorus increased by <0.16 mmol/L (0·5 mg/dL) from baseline on a single measurement.

b Oral phosphate dose is 20-60 mg/kg per day divided into three to five doses per day, and alfacalcidol 40-60 ng/kg per day or calcitriol 20-30 ng/kg per day. Depending on the formulation, the active vitamin D could be given one to three times a day.

c Patients were enrolled sequentially into cohorts defined by the initial dose of burosumab. Within each cohort, patients were randomized to Q2W or Q4W regimen i.e. Dose Cohort 1 received initial doses of 0.1 mg/kg Q2W or 0.2 mg/kg Q4W, Dose Cohort 2 received initial doses of 0.2 mg/kg Q2W or 0.4 mg/kg Q4W; Dose Cohort 3 received initial doses of 0.3 mg/kg Q2W or 0.6 mg/kg Q4W. During the titration period (16 week), dose was adjusted every 4 weeks in 0.3mg/kg increments to meet serum phosphorus targets.

d Burosumab initiated at 0·8 mg/kg Q2W and dose was increased to 1.2 mg/kg at any time during the study when a patient met all the dose-adjustment criteria: 2 consecutive serum phosphorus measurements below the normal range; serum phosphorus increased by <0.5 mg/dL from Baseline; and the patient had not missed a dose of study drug that would have accounted for the decrease in serum phosphorus.

e the submission reported (p34) that data are now available to a maximum of 124 weeks of treatment and follow up, however results up to only 88 weeks are presented in the submission.

6.8 All studies were multicentre (CL301 included one study site in Australia) and had an open-label design. The duration of formal treatment in all studies was 64 weeks, followed by open label extension where all patients received burosumab. The primary assessment of outcomes was at 40 weeks with an additional assessment at 64 weeks. While extended follow up data to 88 weeks is available from CL301, the data beyond the 64 week randomised period is contaminated by cross over and included only 6 patients originally randomised to burosumab. CL201 included two treatment extension periods: (i) all patients receive burosumab every 2 weeks (Q2W) from Week 64 to Week 160 for efficacy, and (ii) patients continue burosumab up to Week 214 for safety. Patients in the included studies were between 1 and 12 years. There was no clinical trial evidence presented for patients younger than 1 year of age or for those between the ages of 13 and 17 years (inclusive). The PSCR noted that several real world studies, which were not of the same quality as the evidence pertaining to

patients aged 1 to 12, were available for patients aged between 13 and 17 which provided reassurance that an improvement in key biochemical parameters was observed across childhood and adolescence (see paragraph 6.27).

6.9 The dose regimen for CL301 and CL205 was based on data from CL201, which established that burosumab 0.8 mg/kg every 2 weeks (Q2W) administered for 40 weeks increased biochemical parameters associated with XLH.

6.10 There were differences in the baseline characteristics of patients across the studies (given differences in eligibility criteria) in terms of patients' age (younger in CL205), physical characteristics (smaller in CL205), duration of prior conventional therapy (longer in CL201) and RSS total score (higher mean score in CL301 indicating more severe rickets). In CL201, 3 (6%) patients were enrolled without radiographic rickets (RSS=0). The proportion of patients with RSS ≥ 1.5 in the burosumab Q2W arm was 65.4% (17/26) in CL205 and 92% (12/13) in CL201, with the proportion of patients with RSS ≥ 2 was not reported in CL201 and 76.9% (10/13) in CL205. In CL301, all patients had an RSS ≥ 2 at study enrolment.

6.11 The overall risk of bias in the three included studies was low to moderate due to the open-label design. The evaluation of subjective outcomes such as patient reported outcomes (pain, fatigue or physical function) or adverse events (AEs) may be affected by reporting bias, particularly for within-group comparisons to baseline. The assessment of the RSS and RGI-C outcomes were conducted by independent radiologists blinded to patient identity, treatment assignment and timing of radiographs, which would limit bias to these outcomes. Other efficacy outcomes such as biochemical PD parameters and growth (in height or recumbent length) were objective assessments.

Comparative effectiveness

6.12 The submission stated the main goal of treatment in XLH with burosumab was to address the pathophysiology of excess FGF23 and improve phosphate homeostasis, consequently improving bone health, physical function, mobility and pain and reducing complications. Therefore, the submission nominated the relevant outcomes to be: (i) clinical assessment of rickets (RSS and RGI-C) and growth (changes in standing height or recumbent length); (ii) biochemical assessment of phosphate homeostasis and bone mineralisation (serum phosphate, serum 1,25(OH)2D, ALP and renal phosphate reabsorption (TmP/GFR); and (iii) mobility and physical function assessment (six-minute walk test, 6MWT).

6.13 All studies presented RSS and RGI-C as a primary or secondary efficacy outcome and reported results at Week 40 and Week 64. Rickets severity, assessed by the RSS, was the only trial outcome included in the submission's modelled economic evaluation (see Economic Analysis).

6.14 The NICE UK[3] noted that RSS and RGI-C are measures which quantify the clinical effectiveness of burosumab in children, but that other outcomes are also relevant to capture manifestation of XLH beyond rickets. RSS and RGI-C focus on bone manifestations of XLH and do not capture other important aspects of XLH such as changes in the metabolic manifestations of XLH, XLH symptoms or progression such as pain, fatigue and dental problems. In addition, while RSS captures changes in rickets it does not capture changes in bone defects (such as bowing of arms and legs) which is an important XLH symptomology, and can affect a patient's ability to walk, pain level, growth, fatigue, dental problems and quality of life. The PSCR noted that NICE also considered that "in the absence of an alternative measure….RSS was an acceptable and measurable proxy for disease severity and progression in people with XLH".

6.15 RSS assessment is performed at isolated time points, thus is limited by comparison with available prior radiographs, which may prevent detection of small changes. The RGI-C assesses changes in a side-by-side comparison of radiographs. While the RSS is a quantitative measure, the RGI-C provides a complementary qualitative evaluation of radiographic changes, with significant correlations between the two scales (Whyte et al 2018).[4]

6.16 The RSS was constructed to measure rickets severity in the wrists and knees based on the degree of metaphyseal fraying and cupping and the proportion of growth plate affected. It is a 10-point scale (four points for the wrists and six points for the knees), in which higher scores indicate more severe rickets. A study investigating the relationship between the RSS and the severity of clinical and biochemical abnormalities in XLH (Thatcher et al 2019) found that higher RSS is associated with greater biochemical, clinical, and functional impairments in children with XLH. However, at the lower end of the scale (e.g. RSS = 0.5), the RSS may not have adequate sensitivity to detect small changes in XLH due to the 0.5-point increments in the scoring method. Variable thickness of lucency and the proportion of growth plate involvement are given the same score with the RSS, and the assessment software may not allow for < 0.5 increments in the RSS.

6.17 The submission noted that in CL201, RSS response was defined as change from baseline in RSS ≥ -1.0. The clinical importance of this change was unclear given RSS was validated for nutritional rickets and there remain uncertainties around the applicability of RSS in XLH. Across the studies RGI-C response was defined as change in RGI-C global scores ≥ +2.0, which is described as substantial healing of rickets

[3] National Institute for Health and Care Excellence (NICE). 2018. Burosumab for treating X-linked hypophosphataemia [ID1151] – Highly Specialised Technology Evaluation. NICE UK: https://www.nice.org.uk/guidance/hst8/evidence/evaluation-consultation-committee-papers-pdf-6590861101

[4] Whyte MP, Fujita KP, Moseley S, Thompson DD, McAlister WH. 2018. Validation of a Novel Scoring System for Changes in Skeletal Manifestations of Hypophosphatasia in Newborns, Infants, and Children: The Radiographic Global Impression of Change Scale. Journal of Bone and Mineral Research 33(5):868-874.

(Thatcher et al 2019) to indicate improvement of radiographic abnormalities. There is no evidence of established minimally clinically important differences (MCIDs) for RSS and RGI-C. The pre-PBAC response stated that validation studies suggested that a change of -1.0 in the RSS and a score of +2.0 in the RGI-C would be considered clinically important.

6.18 Table 5 presents the key efficacy outcomes reported in CL301, CL201 and CL205.

Table 5: Change from baseline in RGI-C global score and RSS total score and RGI-C and RSS responder at Week 40 and Week 64 in CL301, CL201 and CL205 (ITT)

Outcome	CL301		CL201	CL205
	burosumab Q2W N=29	Conventional N=32	burosumab Q2W N=26	burosumab Q2W N=13
RGI-C global score				
Week 40, LS mean (SE)	+1.92 (0.11)	+0.77 (0.11)	+1.67 (0.12)	+2.21 (0.071)
Difference (95% CI) vs conventional	**1.14 (0.83, 1.45)**		-	
Week 64, LS mean (SE)	+2.06 (0.072)	+1.03 (0.14)	+1.56 (0.11)	+2.23 (0.11)
Difference (95% CI) vs conventional	**1.02 (0.72, 1.33)**		-	
RGI-C response (RGI-C global score ≥ + 2.0, substantial healing)				
Week 40, n (%)	21 (72.4)	2 (6.3)	18 (69.2)	12 (92.3)
Difference % vs conventional	66.2		-	
OR (95% CI)	**39.1 (7.2, 211.7)**		-	
Week 64, n (%)	25 (86.2)	6 (18.8)	15 (57.7)	10 (76.9)
Difference % vs conventional	67.5		-	
OR (95% CI)	**34.1 (5.6, 206.3)**		-	
RGI-C response (RGI-C global score ≥ + 1.0, minimal healing)				
Week 40, n (%)	29 (100.0)	17 (53.1)	11 (88.5)	12 (92.3)
Week 64, n (%)	29 (100.0)	21 (65.6)	21 (80.8)	13 (100.0)
RSS total score				
Baseline, mean (SD)	3.17 (0.98)	3.19 (1.14)	1.92 (1.17)	2.92 (1.37)
Week 40, mean (SD)	1.13 (0.72)	2.47 (1.09)	0.75 (0.55)	1.19 (0.52)
LS mean (SE) change from baseline	-2.04 (0.15)	-0.71 (0.14)	-1.06 (0.10)	-1.75 (0.12)
Difference (95% CI) vs conventional	**-1.34 (-1.74, -0.94)**		-	
Week 64, mean (SD)	0.95 (0.72)	2.17 (0.95)	0.81 (0.60)	0.92 (0.49)
LS mean (SE) change from baseline	-2.23 (0.12)	-1.01 (0.15)	-1.00 (0.11)	-2.02 (0.12)
Difference (95% CI) vs conventional	**-1.21 (-1.59, -0.83)**		-	
RSS response (reduction in RSS total scores from baseline ≥ 1.0 points in patients with RSS ≥ 1.0 at baseline)				
Week 40, n (%)	27 (96.4)	14 (43.8)	16 (80.0)	10 (76.9)^
Week 64, n (%)	29 (100.0)	16 (50.0)	16 (80.0)	10 (76.9)^
RSS total score = 0 (completely healed)				
Baseline, n (%)	0	0	1 (3.8)	0
Week 40, n (%)	0	0	7 (26.9)	0
Week 64, n (%)	4 (13.8)	0	7 (26.9)	0

Source: Tables 2.20 to 2.25, pp61-66, Tables 2.28 to 2.30, pp78-81 and Tables 2.34 to 2.35, pp91-92 of the submission.
Abbreviations: ITT=intention-to-treat; LS=least squares; RGI-C=Radiographic Global Impression of Change; RSS=Rickets Severity Score;
^ change from baseline in RSS total scores of ≥1.5 points

6.19 The results demonstrated that:

- There was improved rickets healing in terms of the RGI-C global score and reduction in rickets severity based on the RSS total score at Weeks 40 and 64

across all treatment groups compared to baseline. The mean changes from baseline in RGI-C and RSS at Week 40 for the burosumab Q2W groups were broadly consistent across the included studies. Results at Week 64 were more varied, possibly due to heterogeneity between the studies.

- In CL301, the (least squares mean) change from baseline in RGI-C and RSS at Weeks 40 and 64 were statistically significantly greater in the burosumab Q2W arm than in the conventional therapy arm. The proportion of RGI-C responders reporting substantial healing (RGI-C ≥ +2.0) at Weeks 40 and 64 was also statistically significantly higher in the burosumab Q2W arm than in the conventional therapy arm. The proportion of RGI-C responders (substantial and minimal healing) and RSS responders (reduction from baseline in RSS of ≥ 1.0 points) at Weeks 40 and 64 in the burosumab Q2W arm was numerically higher than in the conventional therapy arm.
- There were a proportion of patients completely healed (RSS total score = 0) in the burosumab Q2W groups (13.8% versus 0% in the conventional therapy arm in CL301, and 26.9% in CL201).

Although the mean changes in RGI-C and RSS in the burosumab Q2W arm compared to the conventional therapy arm of CL301 were statistically significant, it was unclear whether these changes were clinically relevant given there is no established MCID for either scale in XLH.

6.20 In CL301, efficacy in terms of RGI-C and RSS between treatment groups was also analysed in pre-specified subgroups of baseline rickets severity (RSS total score ≤ 2.5 versus > 2.5) and age (< 5 years versus ≥ 5 years). Results demonstrated that efficacy in the subgroups was similar to in the overall study population.

6.21 Results were also presented from the following subgroups: CL301 - RSS ≥ 2.0 (burosumab Q2W n=29 and conventional therapy n=26, post-hoc); CL201 - RSS ≥ 1.5 (burosumab Q2W n=17, pre-specified); and CL205 - RSS ≥ 1.5 (burosumab Q2W n=13, pre-specified). The results demonstrated that the efficacy in terms of RGI-C, RSS and serum ALP were comparable across the studies for patients with XLH aged 1 to 12 years.

6.22 During the treatment extension period, the mean changes in RGI-C and RSS scores were maintained to Week 88 for CL301, although the number of patients providing results for RGI-C and RSS was low (20.7% (n=6) in the burosumab to burosumab arm and 46.9% (n=15) in the conventional therapy to burosumab arm. Changes in RCI-C and RSS scores were also maintained to Week 160 in both CL201 and CL205.

6.23 The results for growth demonstrated increases from baseline in mean standing height/recumbent length Z score, growth velocity and 6MWT at Weeks 40 and 64 in all treatment groups (except for CL205). In CL301, the (least squares mean) change from baseline in height/recumbent length Z score, growth velocity Z score and 6MWT

distance walked at Weeks 40 and 64 were statistically significantly greater in the burosumab Q2W arm than in the conventional therapy arm. In CL205, the effect of burosumab Q2W on change in growth could not be demonstrated (SD was larger than the mean) given the relatively short exposure in a small sample (N=13) of younger population (age 1-4) with variable growth patterns and variability in the assessments.

6.24 In terms of changes in pharmacodynamic markers, all post-baseline mean levels of serum phosphorus, serum 1,25(OH)2D and phosphate reabsorption (except in CL205 which did not assess TmP/GFR) significantly increased and serum ALP (elevated in the presence of rickets) significantly decreased at Week 40 and Week 64 across all treatment groups. In CL301, the (least squares mean) change from baseline in serum phosphorus, serum 1,25(OH)2D, ALP and phosphate reabsorption (TmP/GFR) at Weeks 40 and 64 were statistically significantly greater in the burosumab Q2W arm than in the conventional therapy arm.

6.25 The submission also presented results of patient reported outcomes from CL301 and CL205. In CL301, pain was assessed using the Faces Pain Scale – Revised (FPS-R) and PROMIS pain interference. There was no difference between treatment arms in FPS-R. However, the reduction from baseline in PROMIS pain interference was statistically significantly greater at 40 weeks in the burosumab Q2W arm than with conventional therapy. Improvement in PROMIS physical function mobility and fatigue domains at Weeks 40 and 64 were not statistically different between treatment arms. CL301 and CL201 reported greater improvement from baseline in SF10 physical score than psychosocial scores, and in CL301 the improvement in SF-10 physical score was greater in the burosumab Q2W arm than with conventional therapy. In CL201, there were also increases in sports and physical functioning scales and a decrease in pain as assessed by the POSNA-PODCI, indicating improvement in functional ability and pain at Week 64 and up to Week 160. However, the clinical importance of the improvement in these outcomes is not known as there was no established MCID for these scales in XLH.

6.26 The efficacy results from KRN23-003, a non-comparative study of burosumab Q2W by self-administration in children aged 1 to 12 years with XLH (see paragraph 6.6) demonstrated that for patients treated with burosumab Q2W by self-administration there were non-significant improvements in RGI-C and RSS from baseline at Week 40. However, the sample size of the study was small (N=15) and patients had milder disease compared to CL301 (e.g. mean RSS of 1.29 versus 3.2) and thus, less potential to demonstrate a difference. The study was conducted in Japan therefore may not be applicable to the Australian setting, and the study also indicated potential for the injection to be administered by patients or their carers given there were no noteworthy treatment emergent adverse events (TEAEs) reported after the start of self-administration.

6.27 The submission presented real world evidence from 7 clinical groups in the UK (2 sites), France, Israel, Spain, Saudi Arabia and Argentina. The evidence was presented

in children and adolescents (aged 1-20 years) with XLH primarily in terms of PD outcomes as well as growth, function (6MWT) and quality of life. Overall, the data were generally consistent with the main study results presented in the submission. Based on 12-week response, Dharmaraj et al 2019 indicates that biochemical responses in adolescents (aged 13 to 17 years) treated with burosumab Q2W in the UK were consistent with data in children (aged under 4 years), and these results were comparable to the main studies which included only children 12 years and younger. However, Zhukouskaya et al 2019 demonstrated while biochemical responses were similar between patients < 13 years and ≥ 13 years, the restoration of serum phosphate and phosphate renal reabsorption was slower in adolescents with XLH treated with burosumab. At 6 months, 27% of patients received maximal dose of burosumab (2.0 mg/kg or 90 mg) yet 61.5% of patients did not reach target serum phosphorus level. The study reported that higher doses of burosumab were required to normalise phosphate metabolism in adolescents with XLH, with the mean (SD) final dose of burosumab received at 9 months as 1.2 mg/kg (0.5) and 1.6 mg/kg (0.2) in patients aged < 13 years and ≥ 13 years, respectively.

Comparative harms

6.28 Table 6 summarises the key AEs for the treatment period to Week 64 for CL301 and including the treatment extension results up to Week 214 for CL201 and Week 160 for CL205.

Table 6: Summary of most common adverse events in the main studies

AEs	CL301 Week 64^		CL201 Week 214[a]	CL205 Week 160[b]
	Burosumab Q2W (N=29)	Conventional (N=32)	Burosumab Q2W (N=26)	Burosumab Q2W (N=13)
Any AEs	29 (100.0)	27 (84.4)	26 (100.0)	13 (100.0)
Serious AEs	3 (10.3)	3 (9.4)	0	1 (7.7)
Treatment related AEs	17 (58.6)	8 (25.0)	17 (65.4)	5 (38.5)
Grade 3 or 4 AEs	4 (13.8)	3 (9.4)	1 (3.8)	2 (15.4)
Treatment discontinuation due to AEs	0	0	0	0
Study discontinuation due to AEs	0	0	0	0
Death	0	0	0	0
General disorders and administration site conditions	25 (86.2)	9 (28.1)	23 (88.5)	11 (84.6)
Gastrointestinal disorders	23 (79.3)	17 (53.1)	21 (80.8)	12 (92.3)
Infections and infestations	23 (79.3)	24 (75.0)	25 (96.2)	13 (100.0)
Respiratory, thoracic and mediastinal disorders	21 (72.4)	9 (28.1)	24 (92.3)	11 (84.6)
Musculoskeletal and connective tissue disorders	17 (58.6)	15 (46.9)	17 (65.4)	10 (76.9)
Nervous system disorders	12 (41.4)	9 (28.1)	20 (76.9)	7 (53.8)
Skin and subcutaneous tissue disorders	11 (37.9)	4 (12.5)	14 (53.8)	8 (61.5)
Injury, poisoning and procedural complications	10 (34.5)	2 (6.3)	16 (61.5)	11 (84.6)
Predefined injection site reaction TEAEs	15 (51.7)	-	17 (65.4)	5 (38.5)

Source: Tables 2.37 to 2.46, pp98-111 of the submission.
Abbreviations: AE=adverse event; TEAE=treatment emergent adverse event; Q2W=every 2 weeks;
^ Safety data for the treatment period (Weeks 0 to 64).
a Safety data were evaluated through the end of the study, up to 214 weeks (all patients received burosumab Q2W after Week 64).
b Safety data were evaluated through the end of the study, up to 160 weeks (patients continue to receive burosumab after Week 64).

6.29 In CL301, after 64 weeks of follow up, a higher proportion of patients on burosumab Q2W compared to conventional therapy experienced any AEs, treatment-related AEs and injection site reactions. Across the treatment arms, the incidence of serious AEs was low, most AEs were mild intensity, no patient experienced AEs leading to discontinuation and no deaths were reported. The proportion of patients experiencing AEs in the burosumab Q2W arm of CL301 was generally similar to the proportions in CL201 and CL205.

6.30 In the treatment extension period (results reported at Weeks 66 to 124) of CL301, 20/26 (77%) patients experienced AEs after switching to burosumab Q2W from conventional therapy. However, there were no new safety concerns reported during the treatment extension period.

6.31 The most common reported AEs were symptoms typical to paediatrics (i.e. pyrexia, cough, vomiting, nasopharyngitis, headache and diarrhoea), manifestation of XLH (e.g. arthralgia, pain in extremity, tooth abscess, vitamin decreased) and adverse drug reactions including injection site reactions.

6.32 The PBAC noted that burosumab was associated with more dental caries (31% vs 6%), tooth abscesses (28% vs 9%), diarrhoea (24% vs 6%), cough (51% vs 19%) and arthralgia (45% vs 31%) than conventional therapy.

Benefits/harms

6.33 A summary of the comparative benefits and harms for burosumab versus conventional therapy is presented in Table 7 below. All clinically relevant results are summarised, however the modelled economic evaluation was based solely on RSS results at Week 64.

Table 7: Summary of comparative benefits and harms for burosumab Q2W and conventional therapy – Trial CL301

Benefits							
LS mean change from baseline in RSS and RGI-C							
CL301^	**Burosumab**			**Conventional**			**Mean difference (95% CI)**
	N	**Mean Δ baseline**	**SE**	**N**	**Mean Δ baseline**	**SE**	
RGI-C, Wk 40^	29	+1.92	0.11	32	+0.77	0.11	**1.14 (0.83, 1.45)**
RGI-C, Wk 64	29	+2.06	0.072	32	+1.03	0.14	**1.02 (0.72, 1.33)**
RSS, Wk 40	29	-2.04	0.15	32	-0.71	0.14	**-1.34 (-1.74, -0.94)**
RSS, Wk 64	29	-2.23	0.12	32	-1.01	0.15	**-1.21 (-1.59, -0.83)**
Standing height/ recumbent length Z Score, Wk 64	29	+0.17	0.066	32	+0.02	0.035	**+0.14 (+0.00, +0.29)**
Growth velocity of standing height/ recumbent length (Z Score), Wk 64	29	+1.53	0.26	32	+0.41	0.27	**+1.12 (0.37, 1.88)**
6MWT, Wk 64	29	+75	13	32	+29	17	**+46 (2, 89)**
Serum phosphate (mg/dL), Wk 64	29	+0.98	0.061	32	+0.24	0.058	**0.74 (0.58, 0.91)**
1,25(OH)2D (pg/mL), Wk 64	29	9.89	2.24	32	1.19	2.79	**8.70 (1.72, 15.68)**
TmP/GFR (mg/dL), Wk 64	29	1.16	0.13	32	-0.09	0.07	**1.25 (0.96, 1.54)**
ALP (U/L), Wk 64	29	-174.62	13.43	32	-28.06	19.98	**-146.56 (-191.61, 101.52)**

Harms (Wk 64)						
CL301	**Burosumab n/N**	**Conventional n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Burosumab	**Conventional**	
Any AEs	29/29	27/32	**1.18 (1.01, 1.38)**	100	84.4	**0.16 (0.02, 0.29)**
Treatment related AEs	17/29	8/32	**2.34 (1.20, 4.60)**	58.6	25.0	**0.34 (0.10, 0.57)**
General disorders and administration site conditions	25/29	9/32	**3.07 (1.73, 5.43)**	86.2	28.1	**0.58 (0.38, 0.78)**
Gastrointestinal disorders	23/29	17/32	**1.49 (1.03, 2.17)**	79.3	53.1	**0.26 (0.03, 0.49)**
Respiratory, thoracic and mediastinal disorders	21/29	9/32	**2.57 (1.42, 4.68)**	72.4	28.1	**0.44 (0.22, 0.67)**
Skin and subcutaneous tissue disorders	11/29	4/32	**3.03 (1.09, 8.48)**	37.9	12.5	**0.25 (0.04, 0.46)**
Injury, poisoning and procedural complications	10/29	2/32	**5.52 (1.32, 23.12)**	34.5	6.3	**0.28 (0.09, 0.47)**
Predefined injection site reaction TEAEs	15/29	0	**34.10 (2.13, 545.51)**	51.7	0	**0.52 (0.33, 0.70)**

Source: Compiled during the evaluation from Tables 2.20 and 2.25, pp61-66, Tables 2.28 to 2.30, pp78-81, Tables 2.34 to 2.35, pp91-92, and Tables 2.37 to 2.46, pp98-111 of the submission.

Abbreviations: AE=adverse events; ALP=alkaline phosphatase; LS=least squares; RGI-C=Radiographic Global Impression of Change; RSS=Rickets Severity Score; RD=risk difference; RR=risk ratio; TEAE=treatment emergent adverse event; TmP/GFR=ratio of renal tubular maximum reabsorption rate of phosphate (TmP) to glomerular filtration rate (GFR); 25(OH)2D=1,25 dihydroxy-Vitamin D; 6MWT=Six-minute Walk Test; Q2W=every 2 weeks;

^ Primary outcome of the trial. Main timepoints for trial assessments were Wk 40 (primary outcome, safety), Wk64 (additional efficacy outcomes and safety).

* Safety data for the treatment period (Weeks 0 to 64).

6.34 On the basis of direct evidence presented in the submission in children between ages 1 and 12 years, for every 100 patients treated with burosumab Q2W versus conventional therapy would result in:

- an approximate 1.14 and 1.02 improvement in RGI-C score at Week 40 and Week 64, respectively. However, it is not known whether these differences in RGI-C are clinically meaningful.
- an approximate 1.34 and 1.21 improvement (reduction) in RSS score at Week 40 and Week 64, respectively. However, it is not known whether these differences in RSS are clinically meaningful.
- an approximate +0.14 improvement in standing height/recumbent length (Z score) and +1.12 improvement in growth velocity of standing height/recumbent length (Z score) at Week 64. However, it is not known whether these differences in standing height/recumbent length and growth velocity are clinically meaningful.
- an approximate +46 metre improvement in 6MWT at Week 64. The mean difference in may potentially be clinically relevant given the estimate is higher than the MCID for 6MWT of 31 metres for children.
- an approximate 0.74 mg/dL, 8.70 pg/mL, 1.25mg/dL and -1.46.56 U/L improvement in serum phosphorus, serum 1,25(OH)2D, phosphate reabsorption (TmP/GFR) and ALP respectively and at Week 64. However, it is not known whether these differences in PD outcomes are clinically meaningful.
- approximately 16 more patients experiencing any AE over 64 weeks.
- approximately 34 more patients experiencing treatment related AEs over 64 weeks.
- approximately 58 more patients experiencing general disorders and administration site conditions over 64 weeks.
- approximately 26 more patients experiencing gastrointestinal disorders over 64 weeks.
- approximately 44 more patients experiencing respiratory, thoracic and mediastinal disorders over 64 weeks.
- approximately 25 more patients experiencing skin and subcutaneous tissue disorders over 64 weeks.

- approximately 28 more patients experiencing injury, poisoning and procedural complication over 64 weeks.
- approximately 52 more patients experiencing predefined injection site reaction TEAEs over 64 weeks.

Clinical claim

6.35 The submission described burosumab as superior in terms of effectiveness and superior (and different) in terms of safety compared to conventional therapy comprising oral phosphate and active vitamin D in patients with XLH.

6.36 The ESC considered that the clinical claim for effectiveness of burosumab was supported by the clinical evidence; however, the following caveats applied:

- The studies were small and were limited to children aged 1-12 years, with XLH by RSS (≥ 1.5) who have received prior conventional therapy. The proposed population was for children under the age of 18 years.
- Although the mean differences in RGI-C and RSS at Weeks 40 and 64 were statistically significant for burosumab Q2W compared to conventional therapy, the differences may not be clinically meaningful given the lack of established MCIDs. Patient relevant outcomes (e.g. growth, function, pain and quality of life) were secondary outcomes.

6.37 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.38 The clinical claim of superior safety may not be appropriate as the comparison in practice is an injection versus no injection, and significantly more patients treated with burosumab experienced injection site reactions as well as treatment emergent AEs in the short term (as evident in the clinical studies). However, in the long term, high doses of phosphate and/or calcitriol are known to be associated with complications such as nephrocalcinosis and secondary hyperparathyroidism. The ESC noted that safety findings in the paediatric studies showed manageable AEs with no safety concerns for burosumab. Injection site reactions were the most prevalent treatment emergent AE and were generally mild, manageable, and of short duration. There was also no evidence of hypercalcaemia, hyperparathyroidism, or nephrocalcinosis associated with burosumab treatment in either clinical or post marketing surveillance data.

6.39 The PBAC considered that the claim of superior (and different) comparative safety was not adequately supported by the data.

6.40 The ESC noted that despite extension studies providing some outcome data to Week 160, the long term efficacy and safety of burosumab was uncertain. The ESC considered that this was a particular concern given that treatment with burosumab was likely to be long term.

Economic analysis

6.41 The submission presented a Markov state transition model with four health states defined by RSS: Mild rickets (RSS of 0.5 or 1.0), Moderate rickets (RSS of 1.5 or 2.0), Severe rickets (RSS of 2.5 or more) and Healed rickets (RSS of 0), and Death (to capture background mortality). The analysis conducted was a cost utility analysis comparing burosumab to conventional therapy (oral phosphorus and calcitriol) in children < 18 years with XLH. Table 8 provides a summary of the key components of the economic evaluation.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Burosumab vs conventional therapy
Type of analysis	Cost utility analysis
Outcomes	Quality-adjusted life years (QALYs) gained
Time horizon	Lifetime (100 years), compared to up to 64 weeks of comparative data in the clinical trial.
Patient population	Average age 6.8 years at model start. Patients received burosumab or conventional therapy continuously (assuming full compliance and no early discontinuations) until 18 years of age.
Methods used to generate results	Markov state transition model in Microsoft Excel 2019.
Health states	Four chronic health states defined by Rickets Severity Score (RSS): • Mild rickets (0.5 or 1.0) • Moderate rickets (1.5 or 2.0) • Severe rickets (≥ 2.5) • Healed rickets (0) Plus, Death as an absorbing state accounting for all-cause mortality. No difference in death is assumed between burosumab and conventional therapy.
Cycle length	One year (with half cycle correction applied).
Transition probabilities	• Baseline distribution of patients between health states was informed by pooled data from CL301, CL201 and CL205. • Transition probabilities in the burosumab arm were also based on pooled data from these three studies reflecting change in RSS between baseline and Week 64. • Transition probabilities in the conventional therapy arm were informed by pooled data from the control arm of CL301 and a UK chart review.
Extrapolation	• Constant annual transition probabilities up to age 18 was assumed based on Week 64 study results. • The model also assumed all patients remained in their respective RSS health state beyond age 18, thus assuming the benefit of burosumab would be lifelong. These assumptions are highly uncertain. Little long-term data is available to support these assumptions, the limited longer-term data from the extension studies does not suggest continued improvement, only that gains at Week 64 are maintained with continued treatment up to 160 weeks. Almost all burosumab patients were 'healed' by Year 10 in the model and remained there until death.
Health related quality of life	Health state utilities were derived from a Sponsor-conducted vignette study (no patient reported outcomes from clinical studies or published literature were available). In this utility study, six UK clinicians with experience in treating XLH were asked to rate vignettes of patients with XLH at the following ages: 1-4, 5-12, 13+, 18, 40 and 60 years, based on the four RSS (healed, mild, moderate, severe) health states using the EQ-5D-5L questionnaire. Not all clinical experts valued the 'healed' and 'severe' states, due to lack of clinical experience in these patients. Utility weights were then estimated using an established algorithm using UK weights and were applied by the aforementioned age groups and RSS states in the model.
Costs	Drug cost for burosumab and conventional therapy were based on average dosages CL301, CL201 and CL205 and costed using PBS prices (effective prices for burosumab). Other costs include disease surveillance costs (applied to all patients equally), physiotherapy cost (mild health state only) and surgical

	costs (severe health state only) using appropriate sources. The cost of burosumab varies based on dose used, which in turn depends on cohort average weight and phosphate levels.

Source: Table 3-1, p122 of the submission.

Abbreviations: CADTH=Canadian Agency for Drugs and Technologies in Health; NICE=National Institute for Health and Care Excellence; RSS=Rickets Severity Score; RGI-C=Radiographic Global Impression of Change; XLH=X-linked hypophosphataemia; RSS=Rickets Severity Score; RGI-C=Radiographic Global Impression of Change; ICER=Incremental Cost Effectiveness Ratio; 6MWT=6-minute walk test; HTA=Health Technology Assessment; NICE=National Institute for Health and Care Excellence; SMC=Scottish Medicines Consortium; CADTH=Canadian Agency for Drugs and Technologies in Health.

6.42 Patients entered the model (Cycle 0) from one of the alive health states, based on RSS baseline distribution in pooled CL301, CL201 and CL205 data, at a mean starting age of 6.8 years (also based on the pooled study populations). Patients initiated either burosumab or conventional therapy and were assumed to receive these treatments continuously (i.e. assuming full compliance and no early discontinuation) until 18 years of age. When patients reached 18 years of age, a proportion of patients in each group with persistent rickets continued to receive conventional therapy at an adult dose (i.e. burosumab ceased in all patients).

6.43 At the end of each 1-year cycle, burosumab patients either stayed in the same health state or improved (i.e. they could not deteriorate/transition to a worse health state), whereas patients receiving conventional therapy could deteriorate, as per transition probabilities, up until 18 years of age. Beyond 18 years of age, patients remained in their respective RSS health state for the rest of the model duration until death. Patients could move to the death state from any health state based on age gender specific all-cause mortality. No difference in mortality was assumed between burosumab and conventional therapy, so model transitions were purely driven by RSS and associated assumptions.

6.44 The ESC and PBAC noted that there were a number of uncertainties relating to the model structure, assumptions and inputs. These are outlined in paragraphs 6.45 to 6.51.

6.45 RSS health states definition:

- The RSS is unlikely to capture all important aspects of XLH given its focus is limited to bone manifestations. Other aspects of the disease including metabolic manifestations are not captured. In addition, the RSS does not fully capture all bone defects, such as the bowing of the arms or legs, which is an important XLH symptomology, and can affect a patient's ability to walk, pain level, growth, fatigue, dental problems and quality of life. The PSCR stated that rickets is the hallmark feature of XLH in children and reiterated that RSS was the most robust and patient relevant outcome assessed in the trials.
- RSS is measured on a continuous scale (0-10) and little justification was provided in the submission for the health state definitions chosen (beyond "based on expert advice"). There was no evidence provided that demonstrated meaningful differences between the defined health states. The submission based the decision

to use four health states on a seven-level system published by Makitie et al 2003. The PSCR stated that the RSS health states were pragmatically defined and represent the simplification of a complex clinical reality.

- Rickets severity was also assessed using the RGI-C in the clinical studies, but it was not used to define health states in the model. The PSCR stated that RGI-C is a relative measure of effect and cannot be used to define Markov health states.

6.46 Extrapolation:

- Two highly uncertain assumptions were made in the submission regarding the extrapolation of clinical benefit for burosumab:
  1. Annualised transition probabilities (derived from 64 week follow up data) were assumed to remain constant up to an age of 18 years; and
  2. Disease severity was assumed to stabilise from age 18, leading to almost all of the burosumab patients remaining in the 'healed' state from Year 10 until death.
- There was little long-term data provided to support these assumptions. The data from the extension studies suggested that gains at Week 64 were maintained with continued treatment to 160 weeks, but did not suggest continued improvements cycle after cycle beyond the trial period until 18 years of age.
- No data was presented to support the lifelong benefit assumption after stopping treatment at 18 years. The submission stated that this assumption was based on expert clinical opinion that if rickets healed in childhood prior to end of growth, then it is clinically unlikely that the long-term benefits of healing will be reversed. As XLH is a progressive disease, persistent hypophosphataemia (which will continue into adulthood unless treated) is likely to result in further disease progression with symptoms such as osteoarthritis, enthesopathy, stress fractures in weakened bone and dental abscesses, in addition to pain and stiffness which may persist, impacting QoL. The PSCR stated that based on expert clinical opinion, although the withdrawal of burosumab post plate fusion was likely to result in a gradual return of osteomalacia, the return of high FGF23 and low phosphate levels would not result in the bowed long bones or impaired mobility typical of rickets in children.
- The model is highly sensitive to the assumption of continued clinical benefit. Removal of extrapolated treatment effect (by assuming patients do not transition based on RSS score beyond Cycle 2 in the model) resulted in a doubling of the ICER.

6.47 Time horizon:

- While XLH is a lifelong, progressive disease, where diagnosis and management in childhood have lifelong impacts justifying a long model time horizon, the short

durations of follow up in the clinical studies (Week 64 results were used to inform the model) compared to the 100-year time horizon in the model limits the accuracy of any long-term predictions.

- Due to uncertain assumptions around the transitions into the healed rickets health state, the majority of patients in the burosumab arm transitioned into healed rickets by Year 10 and continued to benefit until death. A long-time horizon therefore had the effect of exaggerating this uncertain transition and strongly favoured burosumab. Reducing the model time horizon to 20 years, significantly increased the ICER to > $1,055,000/QALY gained from a base case of $655,000 to < $755,000/QALY gained.

6.48 Population age:

- The population age on entering the model (6.8 years) was based on mean patient age in the pooled clinical studies. Based on the requested restriction, patients would qualify for PBS treatment from birth, whereas the TGA indication restricts use to patients ≥ 1 year of age. As prevalent patients switch to receiving burosumab treatment, the mean starting age of incident patients is likely to trend towards 1 year of age (or mean age of diagnosis).

- While the treatment stopping age of 18 years in the model was consistent with the requested restriction, there is risk for treatment to continue beyond age 18 given burosumab continues to have meaningful benefits beyond rickets and growth in adulthood, such as effects on normalisation of serum phosphorous levels, physical functioning and stiffness. There is also evidence that bone growth may stop earlier than age 18, particularly for girls. Stopping treatment earlier reduces the cost of burosumab (which is a main model driver) but does not affect modelled burosumab effectiveness since the model results predict almost all burosumab patients are 'healed' of rickets by Year 10. See "Transition probabilities" below.

6.49 Burosumab dose:

- The submission stated that the mean burosumab dose in the clinical studies was 0.86 mg/kg up to Week 64 (beyond which the submission considered the data unreliable due to censoring). All patients in the model were therefore assumed to be prescribed this dose (dosed every 2 weeks; adjusted for age and weight as patients moved through the model) and were further assumed to receive treatment with perfect persistence and adherence until 18 years of age. Data was not available to verify the stated mean dose from the pooled clinical studies, but it appeared to be based on average weekly doses reported in CL301 and CL205 where the maximum permitted dose was 1.2 mg/kg every 2 weeks. Given the draft PI permits a maximum recommended dose of burosumab of 2 mg/kg every 2 weeks, the dose in the model likely underestimates costs in the clinical setting. Data available from < 500 patient in the Australian EAP of burosumab reported a

mean weight of 30.9 kg (mean age 10 years) on a mean current dose of 32.45 mg, which would equate to a dose of 1.05 mg/kg. Further, a real-world evidence study conducted by Zhukouskaya et al 2019, found that restoration of serum phosphate and phosphate renal reabsorption in adolescents was slower than in younger patients, despite the use of maximum doses of 2 mg/kg. Therefore, average burosumab doses are likely to be higher in clinical practice than in the model.

6.50 Transition probabilities:

- Transition probabilities were estimated by pooling data from mixed sources: trial CL301 and Phase II studies CL201 and CL205 for burosumab, and trial CL301 and a retrospective UK chart review for conventional therapy. Given the vastly different study designs e.g., prospective versus retrospective, Phase II studies (including dose finding) versus RCT and heterogeneous patient populations, the resultant transition probabilities were likely to be uncertain. Indeed, the estimated annualised transition matrix varied depending on data used. The PSCR stated that CL301 included patients with moderate to severe disease only; therefore, pooled data was used as the model needed to consider a broader range of transition probabilities. The ESC considered that although adding to the uncertainty of the model, the use of pooled data may have been reasonable considering the data available.
- Pooling of study results assumed children of all ages transition with the same probability, and thus implied the treatment effect (of both therapies) was the same regardless of age (when patients are < 18 years). No clinical trial data for burosumab in children aged less than 1 year or between 13 to 17 years (inclusive) was provided to support this assumption.
- It was noted that data from a single patient had informed the transition probability for remaining in the 'healed' state for burosumab patients. Because one patient from CL201 had 'healed' rickets (RSS=0) at study baseline and Week 64, all burosumab patients who transited into the 'healed' state were assumed to remain 'healed' until death. The model was highly sensitive to this transition probability, the base-case ICER doubled if the 'healed' patient experiences mild disease (QALY gain is halved). By contrast, the model assumed that 14% of patients in the conventional therapy arm would transition each year from 'healed' state back to 'severe'.
- The model assumed that burosumab patients could not transition to a worse health state. The PSCR) stated that this was not an assumption, but a reflection of the data from which the transition probabilities were estimated, in which no patient deteriorated while receiving burosumab. The ESC noted that no long-term data was provided to support this assumption when patients ceased burosumab treatment.

6.51 Utilities:

- Given no survival differences were assumed between the two treatment arms, the estimated utility values drive the QALY results. The estimated health state utilities may be uncertain for the following reasons:
  - utility values were derived based on the clinicians' views of XLH symptoms and severity, and therefore, they may not reflect the views of patients, carers or the general public;
  - only six clinicians participated in the sponsor conducted valuation exercise. As a result, there is large variation around the estimated mean utilities. Due to these large variations, the estimated utility value distributions overlap across health states generating anomalies (i.e. the higher end of 'severe' health state distribution may have a higher health state utility than the lower end of 'moderate' health state);
  - not all clinical experts had valued the 'healed' and 'severe' states, due to lack of clinical experience in these patients; and
  - the estimated HRQoL was assumed to decline over time reflecting likely disease progression. However, an increase in health state utilities (across all severities) was observed between ages 18 and 39 years, the reason for this increase was unknown.

Table 9: Utility values used in the economic evaluation

Health state	Utility						Source and nature of estimates
	1-4 years	5-12 years	13-17 years	18-39 years	40-59 years	60+ years	
Healed rickets	0.834	0.909	0.843	0.876	0.840	0.687	Sponsor-conducted utility study using EQ-5D-5L using UK weights.
Mild rickets	0.774	0.757	0.671	0.707	0.643	0.552	
Moderate rickets	0.685	0.613	0.575	0.653	0.586	0.517	
Severe rickets	0.610	0.602	0.479	0.488	0.421	0.282	

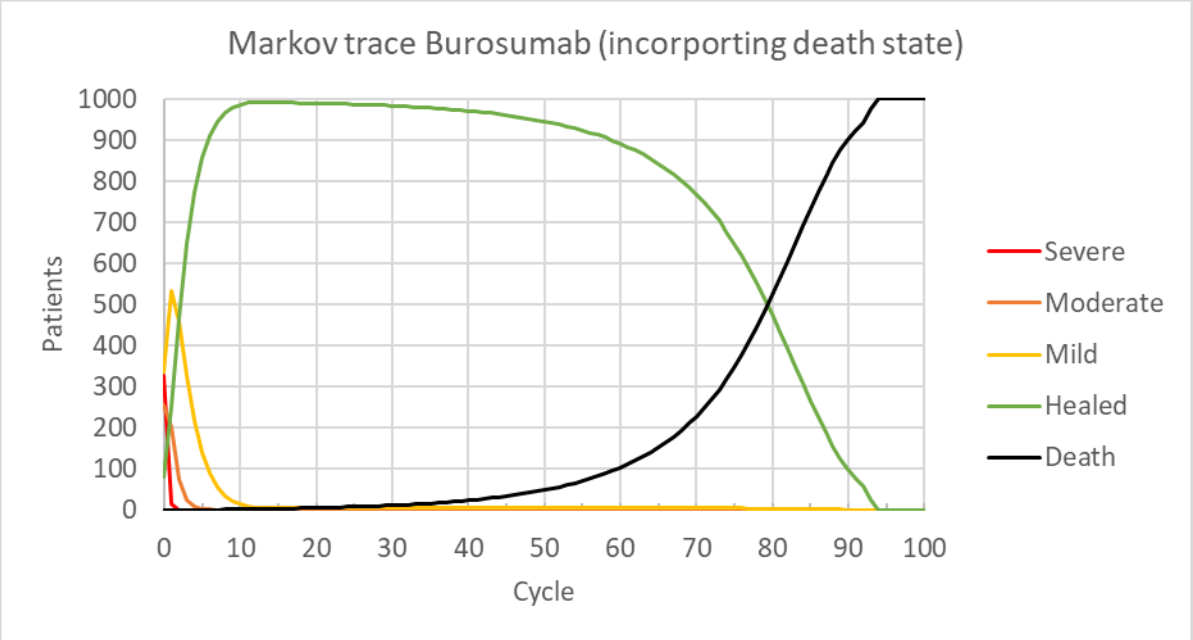
Source: Table 3-5, p130 of the submission.
Healed rickets, RSS=0; Mild rickets, RSS=0.5 or 1.0; Moderate rickets, RSS=1.0 or 2.0; Severe rickets, RSS=≥ 2.5.
Abbreviations: RSS=Rickets Severity Score; EQ-5D-5L= EuroQol-5-Dimension-5-Level.

6.52 The ESC considered that more reliable utility values which more appropriately reflected the health states and the likely disease progression would be required.

6.53 Figures 1 and 2 illustrate the Markov traces for burosumab and conventional therapy, respectively. The major difference between the two treatments is the proportion of patients in the 'healed' health state. Almost all patients (98.3%) in the burosumab arm transitioned to the 'healed' state by Cycle 10 (and remained there until death); however, only 14% of patient in the conventional therapy arm transitioned to the 'healed' state. Despite some initial improvements with conventional therapy, a large proportion of patients continued to have rickets. Death was identical across the two

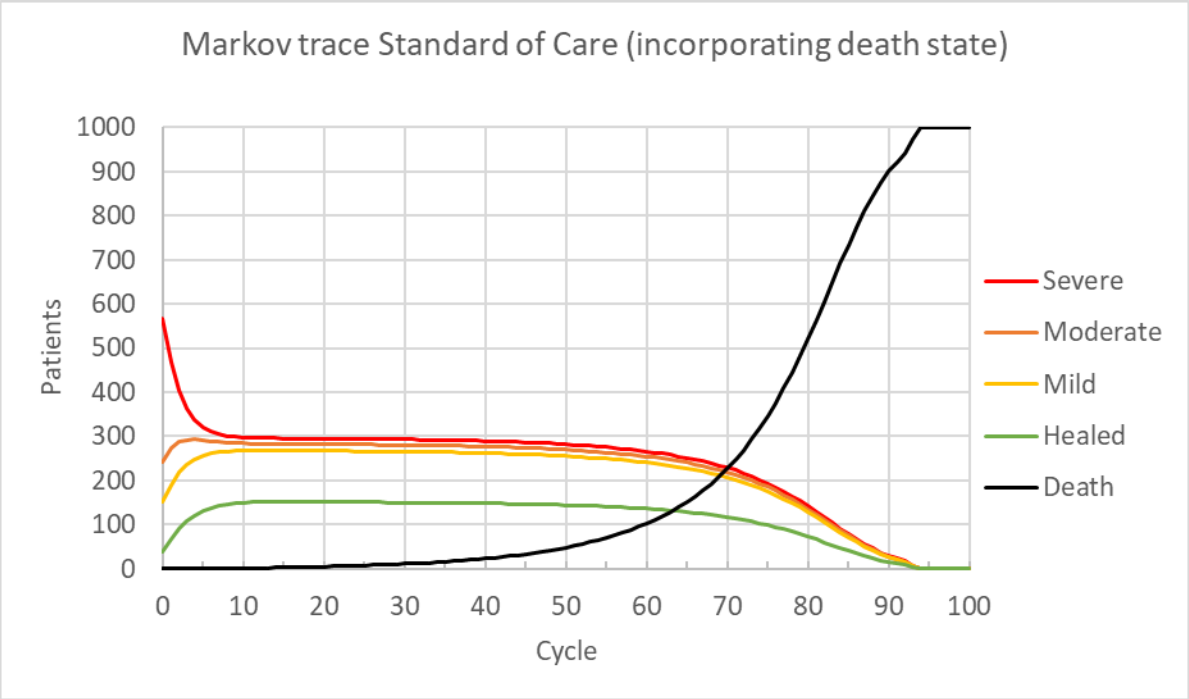
treatment arms, confirming no difference in survival was assumed between burosumab and conventional therapy.

Figure 1. Markov trace for the burosumab arm



Source: generated during the evaluation (adding in Death health state) based on Section 3 Workbook (CEA Model): Trace figures.

Figure 2: Markov trace for the conventional therapy arm



Source: generated during the evaluation (adding in Death health state) based on Section 3 Workbook (CEA Model): Trace figures.

6.54 Table 10 summarises the key drivers of the economic evaluation.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1] /QALY gained
Extrapolation of clinical effect of burosumab	Base case assumptions: Constant annual transition probabilities until age 18 based on Week 64 study results. All patients remained in their respective RSS health states beyond age 18, thus assuming the benefit of burosumab would be lifelong (even after treatment cessation).	Very high, favours burosumab. Removal of extrapolated treatment effect by assuming patients do not transition based on RSS scores beyond cycle 2 in the model resulted in a doubling of the ICER to $[redacted][2]. Building in effect weaning over time by assuming a lower health state utility after treatment cessation, increased the ICER to $[redacted][3].
Transition probabilities	Estimated by pooling data from mixed sources and using favourable assumptions (e.g. burosumab patients can only improve in RSS whereas conventional therapy patients can improve or deteriorate. Only one patient informed the transition for staying healed).	Very high, favours burosumab. The base-case ICER doubles if the one patient who informed the transition for staying healed experiences mild disease (QALY gain is halved). Annualised transition probabilities varied, as does the ICER, if alternate data used. For example, application of CL002 transitions for conventional therapy increases the ICER to $[redacted][3].
Time horizon	Base case: 100 years	Very high, favours burosumab. Reducing the model time horizon to reflect childhood only use (11 years in the model) increased the ICER to $[redacted][2]/QALY.
Burosumab dose	Base case: 0.86 mg/kg	High, favours burosumab. Using a dose of 1.05 mg/kg, based on average dose used in the Australian EAP for burosumab, increased the ICER to $[redacted][3]/QALY.
Age when burosumab treatment is ceased	Base case: 18 years	High, favours burosumab Due to the effect on burosumab cost, increasing stopping age (e.g., if there is leakage of use to the adult population) significantly increased the ICER. Increasing the stopping age to 20 years, increased the ICER to $[redacted][2]. A lower stopping age of 14 years conversely significantly reduced the ICER to $[redacted][4].

Source: compiled during the evaluation.
Abbreviations: XLH=X-linked hypophosphataemia; ICER=Incremental cost effectiveness ratio: QLAY=Quality Adjusted Life Year.
The redacted values correspond to the following ranges:
[1] $655,000 to < $755,000/QALY gained
[2] $1,055,000/QALY gained
[3] $855,000 to < $955,000/QALY gained
[4] $455,000 to < $555,000/QALY gained

6.55 Table 11 presents the results of the economic evaluation. The base case ICER was estimated to be $655,000 to < $755,000/QALY gained.

Table 11: Results of the economic evaluation

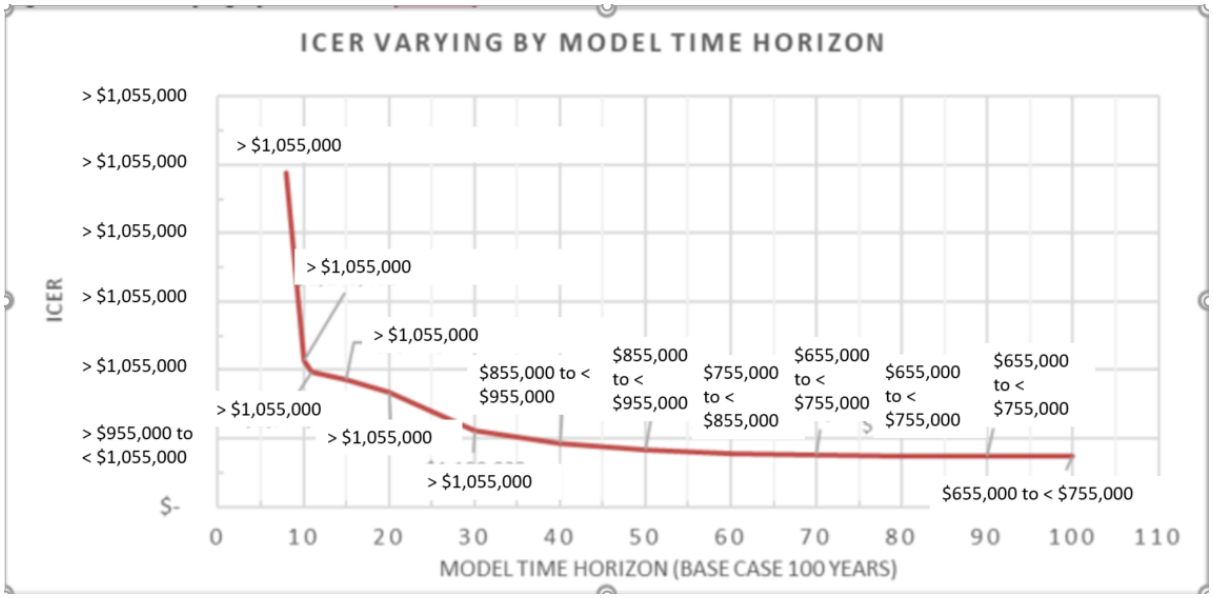
Component	Burosumab	Conventional therapy	Incremental
Total costs	$[redacted]	$47,379	$[redacted]
Total QALYs	17.05	12.92	4.13
		Incremental cost per QALY gained	**$[redacted]**[1]

Source: Table 3-10, p136 of the submission and Analysis worksheet of Section 3 Workbook (CEA Model).
Abbreviations: QALY=Quality Adjusted Life Year;
The redacted value correspond to the following range:
[1] $655,000 to < $755,000/QALY gained

6.56 The ESC considered that the base case ICER was very high and highly uncertain due to the lack of long term data and the significant issues surrounding the definition of health states, the number of assumptions made in relation to the transition probabilities and extrapolation, the long time horizon and the derivation of the utility values.

6.57 Figure 3 plots the ICER against the time horizon. Due to the small estimated incremental QALYs, the model is very sensitive to changes in time horizon below 50 years.

Figure 3. ICER varying by model time horizon



Source: generated during evaluation based on Section 3 Workbook (CEA Model).

6.58 The results of key univariate sensitivity analyses are summarised below. The results indicate that the model is most sensitive to time horizon, treatment stopping age, burosumab dose, transition probabilities for burosumab and conventional therapy, extrapolation of burosumab treatment effect and price of burosumab.

Table 12: Results of sensitivity analyses including additional analyses conducted during the evaluation

Analyses	Incremental cost	Incremental effectiveness	ICER
Base case	**$** [redacted]	**4.13**	**$** [redacted] **/ QALY**
Time horizon (base case: 100 years)			
11 years (childhood only)	$ [redacted]	0.51	$ [redacted]
20 years	$ [redacted]	1.82	$ [redacted]
50 years	$ [redacted]	3.70	$ [redacted]
Mean age at baseline (base case: 6.8 years)			
2 years	$ [redacted]	4.07	$ [redacted]
10 years	$ [redacted]	4.09	$ [redacted]
Treatment stopping age (base case: 17 years)			
14 years	$ [redacted]	4.13	$ [redacted]
20 years	$ [redacted]	4.13	$ [redacted]
Age 15 in girls and 17 in boys (when it is estimated that epiphyseal closure occurs, on average)	$ [redacted]	4.13	$ [redacted]
Continued treatment to 65 years of age (i.e. leakage to adult population)	$ [redacted]	4.13	$ [redacted]
Burosumab dose (base case: 0.86 mg/kg)			
0.8 mg/kg	$ [redacted]	4.13	$ [redacted]
1.05 mg/kg (as per mean dosage in Australian AEP)	$ [redacted]	4.13	$ [redacted]
1.2 mg/kg	$ [redacted]	4.13	$ [redacted]
2 mg/kg (maximum allowable dose)	$ [redacted]	4.13	$ [redacted]
Burosumab SPA rebate (base case: [redacted]%)			
[redacted]%	$ [redacted]	4.13	$ [redacted]
[redacted]%	$ [redacted]	4.13	$ [redacted]
Transition probabilities for burosumab 'healed' to 'healed' state (base case: 100% based on result for 1 patient)			
(The) one patient moves to 'mild' health state	$ [redacted]	2.08	$ [redacted]
Transitions same as conventional therapy	$ [redacted]	2.37	$ [redacted]
Extrapolation of burosumab treatment effect (base case: assume constant transition probabilities to age 18 years)			
Removal of extrapolated transition probabilities (assuming no further health state transitions beyond cycle 2 in the model except for background mortality)	$ [redacted]	2.14	$ [redacted]
Assume patient discontinue burosumab after 5 years then follows transitions in conventional therapy arm	$ [redacted]	1.00	$ [redacted]
Transition probabilities for conventional therapy (base case: based on CL301 and UK chart review)			
Based on CL002 study only	$ [redacted]	3.32	$ [redacted]
Life time treatment effect assumption adjusted so that treatment effect wanes over time (by altering utility values) from age 19 to 30 years (base case: utility values remain constant)			
From 19 years of age (after burosumab treatment cessation), apply utilities according to the following: - Mild (base case) values to the Healed state - Moderate (base case) values to the Mild state - Severe (base case) values to the Moderate state - Applied average decrement of the above three changes to the Severe health state.	$ [redacted]	3.45	$ [redacted]
Applied as per the above, but from 30 years of age	$ [redacted]	3.74	$ [redacted]

Source: Table 3-12, p137 of the submission, additional analyses were performed as described using Excel model provided with the submission.

Italics indicates values calculated during the evaluation, if only the estimated ICER is italicised, then the evaluation had obtained a different value compared to result reported in the submission.

Abbreviations: SPA=Special Pricing Arrangement; RSS=Rickets Severity Score;

The redacted values correspond to the following ranges:

[1] *> $1,055,000/QALY gained*
[2] *$755,000 to < $855,000/QALY gained*
[3] *$855,000 to < $955,000/QALY gained*
[4] *$655,000 to < $755,000/QALY gained*
[5] *$455,000 to < $555,000/QALY gained*
[6] *$555,000 to < $655,000/QALY gained*
[7] *> $1,055,000/QALY gained*
[8] *$355,000 to < $455,000/QALY gained*

6.59 The ESC considered that the revisions required to the model structure and utilities were complex, particularly with the expectation that treatment may become life-long. The ESC considered based on the model provided with this submission, further multivariate and univariate sensitivity analyses would be informative, including: use of burosumab beyond 17 years of age, and maintenance of improvement beyond the trial evidence instead of improvement up to the age of 18. However, it was acknowledged that given the available data and proposed patient population, a high level of uncertainty would remain with these model revisions.

6.60 Noting the very high ICER, the ESC considered that any adjustments to the economic model and the proposed price of burosumab should account for the uncertainties in the model structure, assumptions applied and available data.

Drug cost/patient/year

6.61 The drug cost per patient per year for burosumab is dependent on the assumed dose. At the assumed average dose of 0.86 mg/kg the drug cost per patient per year for burosumab ranged from $[redacted] to $[redacted] (using effective prices and weights by age/sex distribution derived from the Australasian Paediatric Endocrine growth charts).

6.62 The costs used in the trial, model and financial estimates for burosumab are reasonably consistent; however, can change significantly depending on the dose of burosumab used (which is dependent on patient weight, dosage and phosphate levels).

Estimated PBS usage & financial implications

6.63 This submission was considered by DUSC.

6.64 The submission estimated the financial implications of the proposed listing using an epidemiological approach based on data of XLH prevalence from the UK General Practice Research Database study, which was considered consistent with the Australian EAP for burosumab (commenced September 2018) that had enrolled 55 paediatric patients. DUSC noted that the prevalence of disease in Australia might differ to that in the UK and considered that there were limitations with the UK data which included that no genetic, radiological or blood tests were used to identify or confirm cases. The pre-PBAC response acknowledged that there was very little available evidence to inform prevalence estimates in the Australian population, but stated that an Australian prevalence study was nearing completion.

6.65 The submission assumed burosumab would only substitute for conventional therapy comprising oral phosphorus and calcitriol, with a small cost-offset, and all patients commencing burosumab will continue treatment with 100% compliance.

6.66 Table 13 summarises the key inputs in the financial estimates.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent with XLH	0.0017% Source: UK General Practice Research Database (GPRD), *Hawley et al 2020*	Reasonable given lack of Australian data. Literature has also reported increasing prevalence of XLH over time[5]. However, the DUSC considered the estimate of 0.0017% was an underestimate as 16 and 17 year olds were not included in the estimate and the estimate likely only identified severe cases. The pre-PBAC response indicated that data would be forthcoming from an Australian study to estimate prevalence of XLH in Australia[6].
Uptake rate of burosumab	Yr 1: 70%, Yr 2: 80%, Yr 3 to Yr 6: 90% Source: Assumption	The assumption could not be verified. DUSC considered that uptake would be high in newly diagnosed patients. The pre-PBAC response stated that experience in the EAP suggested that uptake would be high.
Compliance for burosumab	100% Source: Assumption	This was consistent with 0% discontinuation assumed in the economic evaluation and the clinical data. The pre-PBAC response stated that experience in the EAP suggested that compliance and persistence with burosumab would be high.
Compliance for conventional therapy	75% Source: Assumption	The assumption could not be verified, however clinical data from CL301 reported no discontinuations in the conventional therapy group during the 64-week treatment period. Nonetheless, the financial estimates were not sensitive to the compliance rate for conventional therapy.
Burosumab dose	0.86 mg/kg Q2W Source: Section 3.6, *based on included studies.*	As discussed in Economic Analysis, this may be an underestimate of the likely prescribed dose as the mean dose from the Australian EAP data was 1.05 mg/kg.

[5] Hawley, S., Shaw, N. J., Delmestri, A., Prieto-Alhambra, D., Cooper, C., Pinedo-Villanueva, R., & Javaid, M. K. (2020). Prevalence and Mortality of Individuals With X-Linked Hypophosphatemia: A United Kingdom Real-World Data Analysis. The Journal of clinical endocrinology and metabolism, 105(3), e871–e878. https://doi.org/10.1210/clinem/dgz203

[6] X-Linked Hypophosphataemic Rickets (XLH) Prevalence Study, A one-off survey conducted by the Australian Paediatric Surveilance Unit (APSU) Study protocol, Commenced June 2020, available from: https://www.apsu.org.au/assets/current-studies/XLH-Prevalence-Protocol-V3-June-2020.pdf, accessed 6 Jan 2021.

<table>
<tr><th>Parameter</th><th>Value applied and source</th><th>Comment</th></tr>
<tr><td>Conventional therapy dose</td><td>Oral phosphate: 4 x 500 mg tablets per day
Calcitriol: 25 ng/kg per day
Source: Section 3.6 based on guidelines, PI, trial and expert advice</td><td>The doses were consistent with the economic evaluation. The assumed doses did not account for variations across the weight-based dosing. The submission used a fixed dose of phosphate for all patients, which was not entirely consistent with the main trial and clinical guidelines. The weight-based dosing of calcitriol was within the range recommended by the guidelines but lower than the mean dose in the main trial, furthermore the average dose was rounded up to 250 ng (see below). In CL301 the mean daily dose by body weight for phosphate was approximately 41 mg/kg and calcitriol 30 ng/kg, and the guideline# recommended doses for phosphate is 20–60 mg/kg daily given 4-6 times per day in young patients and for calcitriol 20-30 ng/kg daily in 2-3 divided doses or 50 ng daily in patients >12months adjusted on the basis of clinical and biochemical responses.</td></tr>
<tr><td>Patient weight (kg)/age distribution</td><td><table><tr><th>Age</th><th>Mean weight</th></tr><tr><td>1</td><td>10.48</td></tr><tr><td>2</td><td>12.74</td></tr><tr><td>3</td><td>14.24</td></tr><tr><td>4</td><td>16.72</td></tr><tr><td>5</td><td>18.24</td></tr><tr><td>6</td><td>20.74</td></tr><tr><td>7</td><td>23.00</td></tr><tr><td>8</td><td>26.00</td></tr><tr><td>9</td><td>28.76</td></tr><tr><td>10</td><td>32.52</td></tr><tr><td>11</td><td>36.78</td></tr><tr><td>12</td><td>41.52</td></tr><tr><td>13</td><td>46.00</td></tr><tr><td>14</td><td>50.45</td></tr><tr><td>15</td><td>53.91</td></tr><tr><td>16</td><td>57.34</td></tr><tr><td>17</td><td>60.72</td></tr></table>Source: Australasian Paediatric Endocrine Group (APEG) growth charts for boys and girls in Australia and New Zealand. Averaged across boys and girls assuming a 47.7% to 52.3% gender split.</td><td>Reasonable and consistent with the economic evaluation. The submission determined the average dose of burosumab treatment (rounded to nearest 10 mg) by body weight/age calculated as the mean dose multiplied by the mean body weight by age distribution in the Australian population. The XLH population is likely to be of smaller stature (and lower body weight) than the general population at the same age, due to effects on growth. XLH is also likely to be more prevalent in girls given it is an X chromosome linked disease. Both would lead to a lower burosumab dose, despite this overall dose of burosumab is still likely to be overestimated due to a potential underestimate of the prescribed mean dose for burosumab.</td></tr>
</table>

Parameter	Value applied and source	Comment
Population weighting	Age / Weighting 1 6.11% 2 6.05% 3 5.99% 4 5.77% 5 6.07% 6 5.97% 7 5.95% 8 6.02% 9 5.96% 10 5.94% 11 5.96% 12 5.88% 13 5.88% 14 5.83% 15 5.65% 16 5.48% 17 5.47% Source: Calculated based on Y1 (2020) ABS population distribution by age (*i.e., base population by age / total population 1-17 years)*	The submission derived the population weighting to estimate the average number and strengths of treatment units (e.g. vials) required per dose in the population distribution by body weight/age. The submission inappropriately assumed the population weighting based on the Yr (2021) ABS population distribution by age for all 6 years of listing. Age distribution in the general population may not reflect age distribution of patients with XLH. Furthermore, DUSC noted that the pattern of use is likely to change over time with older prevalent patients getting treated initially and younger patients in later years as incident (newly diagnosed patients) are treated. A higher proportion of older patients will increase total mg of burosumab needed and increase cost to PBS and vice versa.
% burosumab packs split by population weight/age distribution	burosumab / % population split 10mg 23.92% 20mg 81.76% 30mg 28.51% Source: Calculation based on Section 3.6 *Sum of age/weight distribution (population weighting x number of burosumab vials by strength)*	The submission estimated % burosumab pack split was simplistic and did not account for variations across the weight-based dosing and the required number packs or strengths. Sensitivity analysis was conducted assuming average weight ±20%.
Calcitriol capsules (250 ng) / day by population weight/age distribution	3.78 Source: Calculation based on Section 3.6 Sum of age/weight distribution (population weighting x number of calcitriol capsules)	The average number of capsules per day may be an overestimate given the submission weight-based dosing of calcitriol was rounded up to 250 ng, however sensitivity analysis indicated the estimates were not sensitive to the average calcitriol capsules / day.
Burosumab scripts / year	13.04 Source: Compliance (100%) x duration (13.04 months) x doses/month (2) / pack size (2)	
Conventional therapy scripts / year	Oral phosphate: 10.95 Calcitriol: 10.35 Source: Compliance (75%) x duration (13.04 months) x doses/month (112 phosphate and 105.9 calcitriol) / pack size (100)	The estimates were simplistic and did not account for variations in weight-based dosing.
Substitution rate burosumab : conventional therapy	1 : 1 Source: Assumption	The submission assumed all eligible patients initiating burosumab would otherwise receive conventional therapy.
MBS cost	$17.75 Source: MBS item 3 (100%)	Reasonable.

Source: Constructed during the evaluation from pp139-142 of the submission and parameters in the Section 4 Workbook (Financial Impact).xlsx.

Abbreviations: SC=subcutaneous; Q2W=every 2 weeks; XLH=X-linked hypophosphataemia;

Haffner D et al. 2019. Clinical practice recommendations for the diagnosis and management of X- linked hypophosphataemia: Consensus Statement. Nature Reviews Nephrology 15(7):435-455.

6.67 Table 14 summarises the estimated net financial implications to the PBS for the proposed listing of burosumab for XLH over the first six years (assumed 2021-2026) of listing, based on: (i) the estimated Australian population (age 1 to 17); (ii) XLH prevalence rate of 1.7 per 100,000 paediatrics; (iii) assumed uptake rates for burosumab; (iv) mean dose 0.86 mg/kg (from study CL301); and (v) assumed 100% compliance (0% discontinuation).

Table 14: Estimated use and financial implications to the PBS/RPBS[a] for the proposed listing of burosumab using effective prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of number of treated patients						
Australian population (age 1-17)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Eligible patients with XLH confirmed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
burosumab Uptake rate	70%	80%	90%	90%	90%	90%
Total patients treated with burosumab	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimation of the use and financial impact of burosumab						
Total number of burosumab scripts	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
burosumab 2 x 10 mg	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
burosumab 2 x 20 mgs	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
burosumab 2 x 30 mg	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost PBS/RPBS, burosumab	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Estimation changes in use and financial impact of conventional therapy (oral phosphate and calcitriol)						
Total number of oral phosphate and calcitriol scripts	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]
Phosphorus 500 mg tablets	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]
Calcitriol 0.25 mcg capsule	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]
Net cost PBS/RPBS, oral phosphate and calcitriol	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]	-$[redacted][6]
Estimated financial implications for the PBS/RPBS and the health budget						
Net change in scripts	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Net change in authorities	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Streamlined	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Written	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net cost PBS/RPBS, proposed listing	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Number of MBS (Item 3) services	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to MBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net change to government budget	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]

Source: Tables 4.1 to 4.5, pp141-142 of the submission and Section 4 Workbook (Financial Impact).xlsx.

Abbreviations: XLH=X-linked hypophosphataemia;

[a] The submission excluded RPBS co-payment from the financial estimates because it is not applicable to burosumab.

The redacted values correspond to the following ranges:

[1] *4,000,000 to < 6,000,000*

[2] *< 500*

[3] *500 to < 5,000*

[4] *$10 million to < $20 million*

[5] *$20 million to < $30 million*

[6] *$0 to < $10 million*

6.68 The net cost to PBS/RPBS was estimated to be $100 million to < $200 million (plus $309,700 net cost to MBS) over the first six years of listing. The DUSC considered that the financial estimates were uncertain given the lack of Australian data on which to base the eligible population and the potentially inappropriate assumptions used in the estimates. For example, the submission assumed that:

- the Year 1 (2020) bodyweight/age distribution in the population would be maintained over the first six years of listing and that age distribution of the PBS XLH population would follow that of the general population (with patient numbers evenly split across all ages < 18 years). However, DUSC noted that it is more likely to see the pattern of use changing over time; initially, prevalent patients are likely to be older and with greater disease duration; however, as the prevalent population is treated, the mean age of incident patients commencing burosumab treatment is likely to be closer to 1 year of age (or age of diagnosis);
- patients would receive an average dose of 0.86 mg/kg which is likely an underestimate. Australian EAP data suggested a mean dose of approximately 1.05 mg/kg. In addition, the submission did not apply weight-based dosing for oral phosphorus. The PSCR stated that the maximum permitted dose in CL301 was lower than that proposed in the draft Product Information and that the prescribed doses may be higher than in the clinical trial and that this would have implications for both the costs and effects of burosumab; and
- there would be 100% compliance and zero attrition, which was conservative.

6.69 Importantly, while the estimates reflected the requested population for burosumab in children and adolescents, the submission ignored the likely leakage of use of burosumab to those beyond age 18 years given burosumab continues to have meaningful benefits outside of rickets and growth into adulthood, such as improving serum phosphorus levels, physical functioning, pain and stiffness.

Financial Management – Risk Sharing Arrangements

6.70 The submission stated that the sponsor is willing to enter into a risk share arrangement to manage uncertainties around the financial estimates, relating to prevalence of XLH in the paediatric population, uptake rate, duration and utilisation and cost of burosumab, with details to be agreed once the final context of listing and the extent of uncertainties are better understood.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend burosumab for the treatment of paediatric patients with X-linked hypophosphataemia (XLH). The PBAC considered that there were complex issues relating to the clinical evidence presented and the proposed

restriction. In addition, the PBAC considered that the incremental cost effectiveness ratio (ICER) was high and likely underestimated and that the financial estimates were highly uncertain.

7.2 The PBAC recognised the high clinical need for effective treatments to treat XLH and that current standard of care was suboptimal. The PBAC noted the strong consumer support for burosumab describing a range of benefits including the ease of administration compared to currently available therapies, the effectiveness of the treatment, the tolerability of the treatment and the improved quality of life associated with the treatment. The PBAC also considered input from XLH Australia Incorporated that had been summarised by the Consumer Evidence and Engagement Unit of the Department of Health from a meeting with XLH Australia Incorporated representatives. This input outlined the impact of the condition on gross motor skills, mental health as well as issues around oral health, pain and need for corrective surgery. The PBAC also noted that the consumer input was strongly supportive of a broad PBS listing across all ages, including adults with XLH. The PBAC considered that the available evidence suggests that all patients may receive some benefit from burosumab, but that this benefit, particularly in adults, needed to be better quantified.

7.3 The PBAC noted that the submission nominated conventional therapy, consisting of oral phosphorus and calcitriol, as the comparator. The PBAC considered that this was appropriate.

7.4 The PBAC noted that the submission was primarily based on one small, randomised clinical trial, CL301 (N = 61), which compared burosumab to conventional therapy in children aged 1 to 12 years of age, with two small, non-comparative studies (CL201 and CL205) presented as supportive evidence. The PBAC noted that a relevant trial, KRN23-003, was inappropriately excluded from the submission as the study treatment was via self-administration (which the PBAC considered would be important for equity of access particularly for rural and remote patients) and that a number of clinical trials were available that evaluated the effects of burosumab in adults.

7.5 The PBAC noted that the population in CL301, CL201 and CL205 (i.e. children aged 1 to 12 years) did not match the population in the proposed restriction (i.e. children up to the age of 18 years). Further, the PBAC noted that the proposed restriction only required patients to have 'confirmed XLH in the patient's medical records'. The PBAC recommended that the restriction include more clinically based criteria such as serum phosphate levels and radiographic evidence of rickets and include confirmation of a PHEX pathogenic variant. In addition, the PBAC recommended that the restriction include continuation criteria which reflected the maintained effects of burosumab.

7.6 The PBAC noted that the primary outcomes presented, and used to quantify the clinical effectiveness of burosumab in children, were the rickets severity score (RSS) and the radiographic global impression of change (RGI-C). The PBAC noted that these

outcomes did not capture aspects of XLH which were important to patients such as changes in gross motor skills, the need for corrective surgery, pain and oral health.

7.7 The PBAC noted that the results of CL301 demonstrated that burosumab was associated with statistically significant changes in RSS and RGI-C at Weeks 40 and 64. However, the PBAC considered the RSS response defined as a ≥ 1 point change was not well justified, and resulted in an 100% response rate for burosumab at 64 weeks compared to 50% response for conventional therapy in trial CL301. The PBAC also noted that the radiological effects of burosumab appeared to be greater than the more patient-relevant effects of growth, the six minute walk test (6MWT), pain, fatigue, mobility, tooth abscesses and dental caries, which for some outcomes favoured the conventional therapy arm (e.g. tooth abscesses) and for others appeared to be no different (e.g. PROMIS fatigue).

7.8 The PBAC, noting that no clinical trial data was presented for children aged 13 to 17 years, considered that for children aged 1 to 12 years of age, burosumab was superior in terms of effectiveness compared to conventional therapy. The PBAC noted that long term effects were unknown given the limited trial data, up to 160 weeks for efficacy and 214 weeks for safety outcomes.

7.9 In terms of safety, the PBAC noted that although the rate of serious adverse events (AEs) and Grade 3 or 4 AEs were similar between burosumab and conventional therapy, burosumab was associated with more dental caries, tooth abscesses, diarrhoea and cough as well as administration site conditions such as pyrexia. The PBAC also noted that long term use of conventional therapy is associated with nephrocalcinosis and secondary hyperparathyroidism. Overall, the PBAC considered that burosumab had a different safety profile compared to conventional therapy with more appreciable short-term side-effects.

7.10 The PBAC noted that the submission presented a cost utility analysis which compared burosumab with conventional therapy in children aged less than 18 years.

7.11 The PBAC considered that the proposed base case ICER of $655,000 to < $755,000 per quality adjusted life year (QALY) gained was highly uncertain and likely highly optimistic. The PBAC noted the limitations with the economic analysis as outlined in paragraphs 6.45 to 6.51, and considered the key limitations were as follows:

- the application of change in RSS as the only modelled outcome. The PBAC considered that the clinical impact of RSS improvement was unlikely to capture patient relevant outcomes. Also, the use of RSS with favourable dichotomisation (healed) appeared to be inconsistent with trial-based patient reported outcomes;
- that the comparative clinical data were derived from heterogeneous sources (pooling of data from CL301, CL201 and CL205 for the burosumab arm and from CL301 and a UK chart review for the conventional therapy arm);
- costs of harms were not considered;

- the average dose applied in the model of 0.86 mg/kg being lower than the mean dose received by children in the Early Access Program (EAP) of 1.05 mg/kg and the maximum dose in the draft Product Information of 2 mg/kg;
- that no supporting clinical trial data for children aged 13 to 17 years was available. The model assumed the benefit in children treated between 13 to 17 years would be the same as that in children treated between 0 and 12 years;
- that annualised transition probabilities, which were derived from 64 week follow up data, were assumed to remain constant up to 18 years. This resulted in almost all burosumab patients entering the 'healed' state by Year 10. In addition, benefits attained by age 18 for patients in the burosumab arm were assumed to remain until death, despite patients stopping treatment at 18 years.

7.12 The PBAC noted that the submission used UK data to estimate the prevalence of XLH in children in Australia. Noting that 55 paediatric patients were enrolled in the EAP, the PBAC considered that the estimated number of paediatric patients (approximately 100 per year) was reasonable. However, the PBAC considered that the estimated financial impact of listing burosumab was likely underestimated due to the:

- Uncertainty in the dose, with lower dosed in the clinical trial than in the EAP as noted in paragraph 7.11;
- application of uptake rates of 70% in Year 1 and 80% in Year 2. The PBAC considered that uptake would be higher in the initial years;
- likelihood that more older, and hence heavier, prevalent patients would be treated initially;
- absence of treatments for harms and adverse events, e.g. dental abscesses; and
- potential for more cases to be identified if burosumab was listed on the PBS and PHEX mutation testing was more readily available.

7.13 The PBAC noted that there were a number of complex issues arising from the submission. Although the benefits of burosumab treatment would likely attenuate with age due to the normal maturation process of bones, the PBAC considered that the restriction should be age agnostic as there is likely to be continued benefits in adults in terms of normalisation of serum phosphate levels, improved physical functioning, fracture healing and reduced stiffness. The PBAC also noted the strong consumer support for an age agnostic listing, the importance of equity of access and that the effects of XLH are lifelong. Therefore, the PBAC recommended that any future submission should present all the available clinical data for burosumab use in children and in adults, including any trials with self-administration, which may be important for equity of access.

7.14 The PBAC recognised that an age agnostic restriction would further affect the cost effectiveness of burosumab. The PBAC, noting that XLH is a rare disease and that

burosumab has a high therapeutic value, considered that a substantial price reduction would be required to address the numerous uncertainties in the model and to achieve a reasonable ICER in the whole XLH population.

7.15 The PBAC also recognised that an age agnostic restriction would affect the utilisation and financial impact estimations. The PBAC considered that data from the Australian prevalence study, which is nearing completion, should be used to inform utilisation estimates in the paediatric and adult populations. In addition, the PBAC considered that a Risk Sharing Arrangement (RSA) which consisted of fixed expenditure caps, beyond which rebates were applied, would be necessary to mitigate risk relating to the financial impact of listing burosumab.

7.16 The PBAC advised that a resubmission, which proposed revised restrictions, presented all available clinical data, included a substantial price reduction and a revised economic evaluation, presented updated utilisation and financial impact estimates, and which presented a proposed RSA for the age agnostic XLH population, could be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway. The PBAC noted that in the pre-PBAC response the sponsor asked that consideration be given to whether burosumab might be suitable for the facilitated resolution pathway. The PBAC considered that there were multiple outstanding issues which needed to be resolved and therefore that a standard re-entry pathway was appropriate.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Kyowa Kirin Australia is disappointed by the decision not to recommend the PBS listing of burosumab (Crysvita) for the treatment of children with X-linked hypophosphataemia (XLH). There is a high clinical need for new treatments for this

condition and Kyowa Kirin will continue to work towards bringing burosumab to XLH patients in Australia.